Neurodegenerative disorders

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Neurodegenerative disorders

- **The incidence and social impact of neurodegenerative brain disorders in ageing populations has resulted in a massive research effort in recent years, and the improved understanding of the molecular basis of these disorders now offers real hope for therapeutic progress in the not-too-distant future.**

Neurodegenerative disorders

- **As a rule, dead neurons in the adult CNS are not replaced, nor can their terminals regenerate when their axons are interrupted. Therefore, any pathological process causing neuronal death generally has irreversible consequences.**

- **At first sight, this appears to be very unpromising territory for pharmacological intervention, and indeed drug therapy currently has rather little to offer, except in the case of Parkinson's disease.**

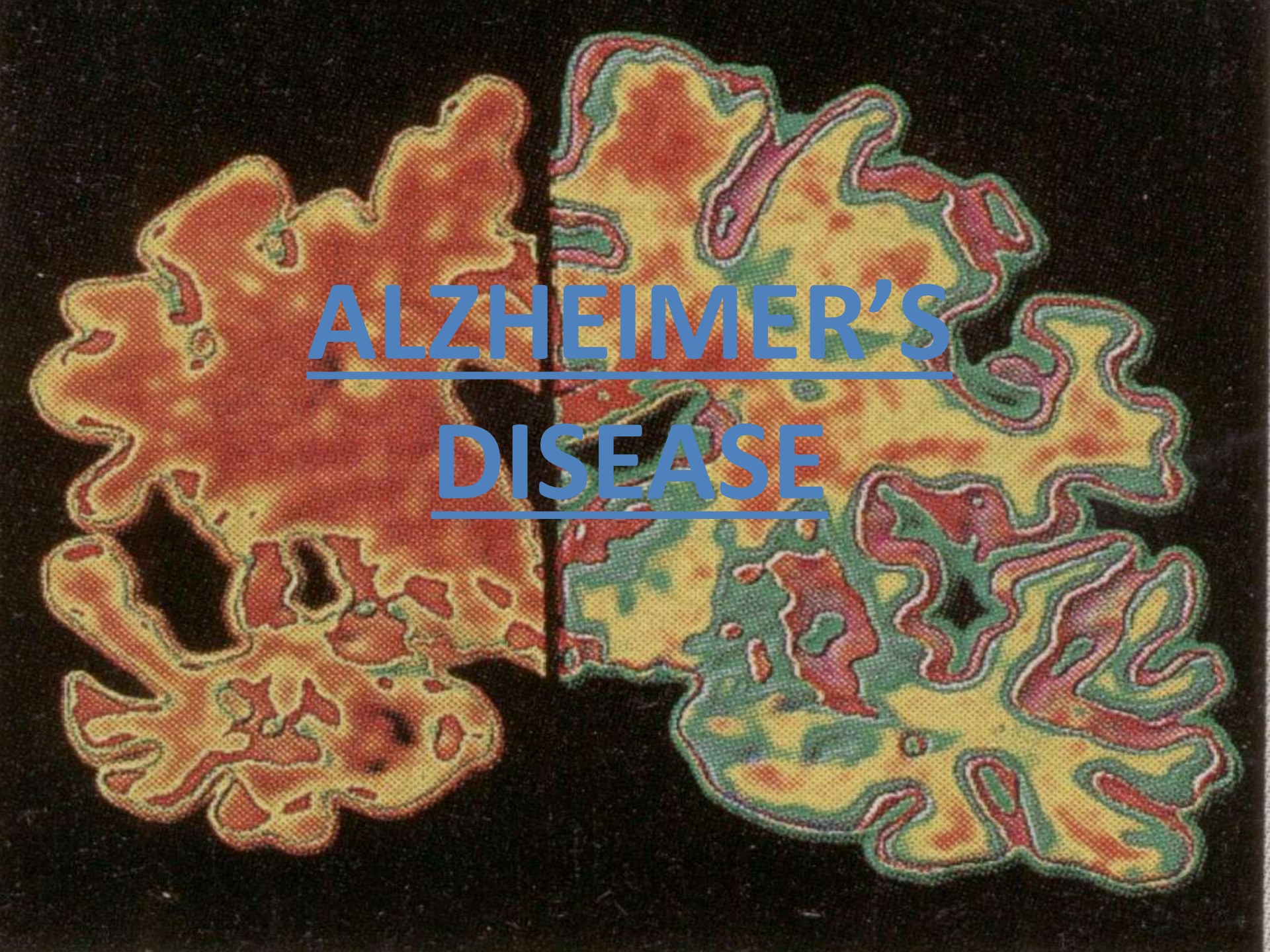
Neurodegenerative disorders

- **The discussion focuses mainly on three common neurodegenerative conditions, namely dementia (Alzheimer's disease), ischaemic brain damage (stroke) and Parkinson's disease**

- **The mechanism discussed would be responsible for neuronal death, focusing on protein deposition (amyloidosis), excitotoxicity, oxidative stress and apoptosis**

- **Pharmacological approaches (so far hypothetical) to preventing neuronal loss**

- **Pharmacological approaches to compensation for neuronal loss.**


ALZHEIMER'S
DISEASE

THOSE WHOSE LIVES IT HAS CLOUDED

Ronald Reagan

At 89, six years after his diagnosis, he no longer remembers being President but continues to raise public awareness of Alzheimer's

DIRCK HALSTEAD FOR TIME

Rita Hayworth

The disease stripped this '40s siren of her glamour and took her life at age 68; her daughter holds galas to raise millions for research

Iris Murdoch

The brain of the Irish-born philosopher-novelist who gave us *Under the Net* was donated to science

PETER JORDAN—AFP

Sugar Ray Robinson

Called "pound for pound, the best fighter," the five-time middleweight world champ died with Alzheimer's, heart disease and diabetes

E.B. White

The master essayist and storyteller lost his gift of words and died at 86

Aaron Copland

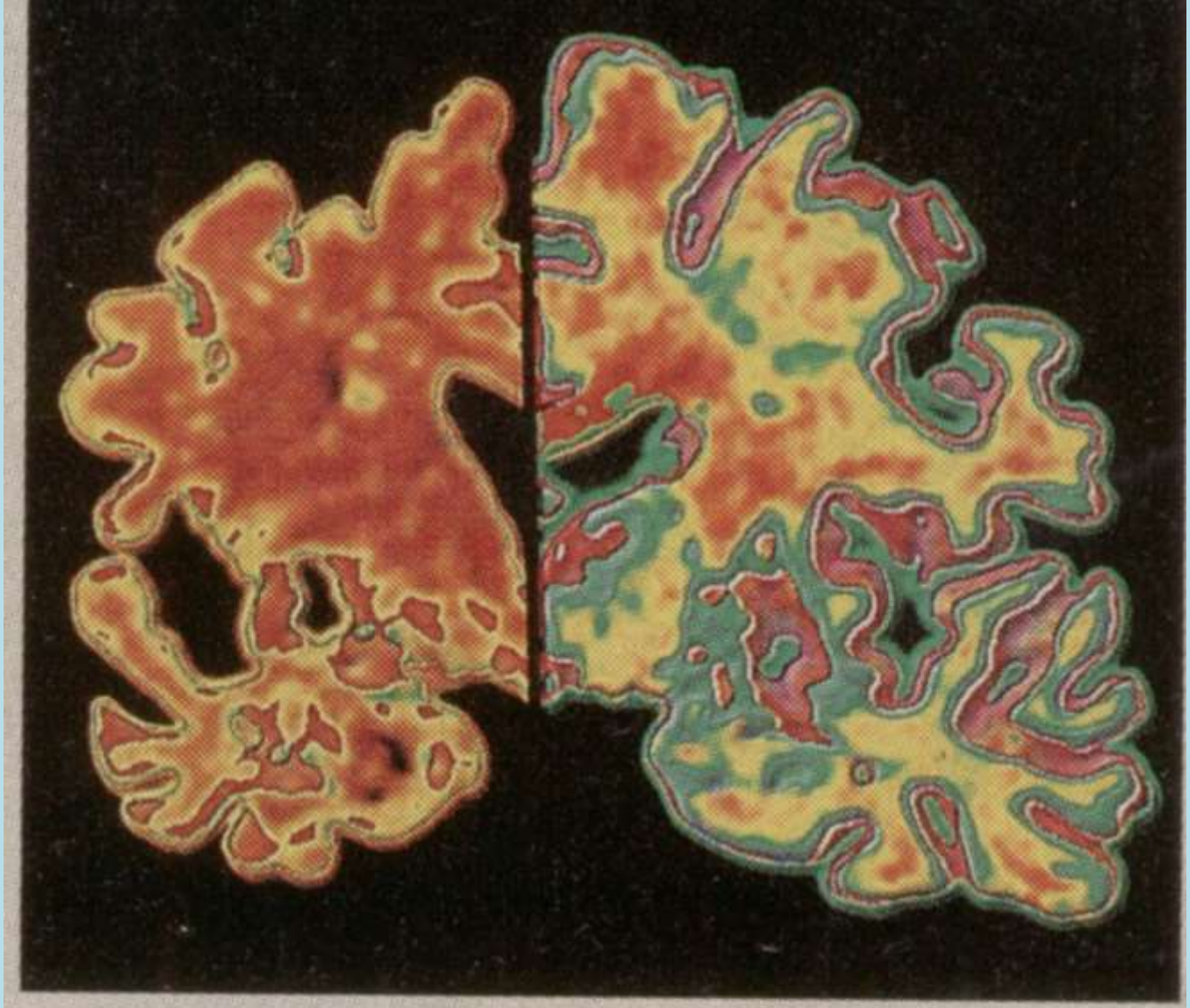
The Brooklyn-born composer of folksy American jazz died of Alzheimer's at 90

JOHAN ELBERS—TIMEPIX

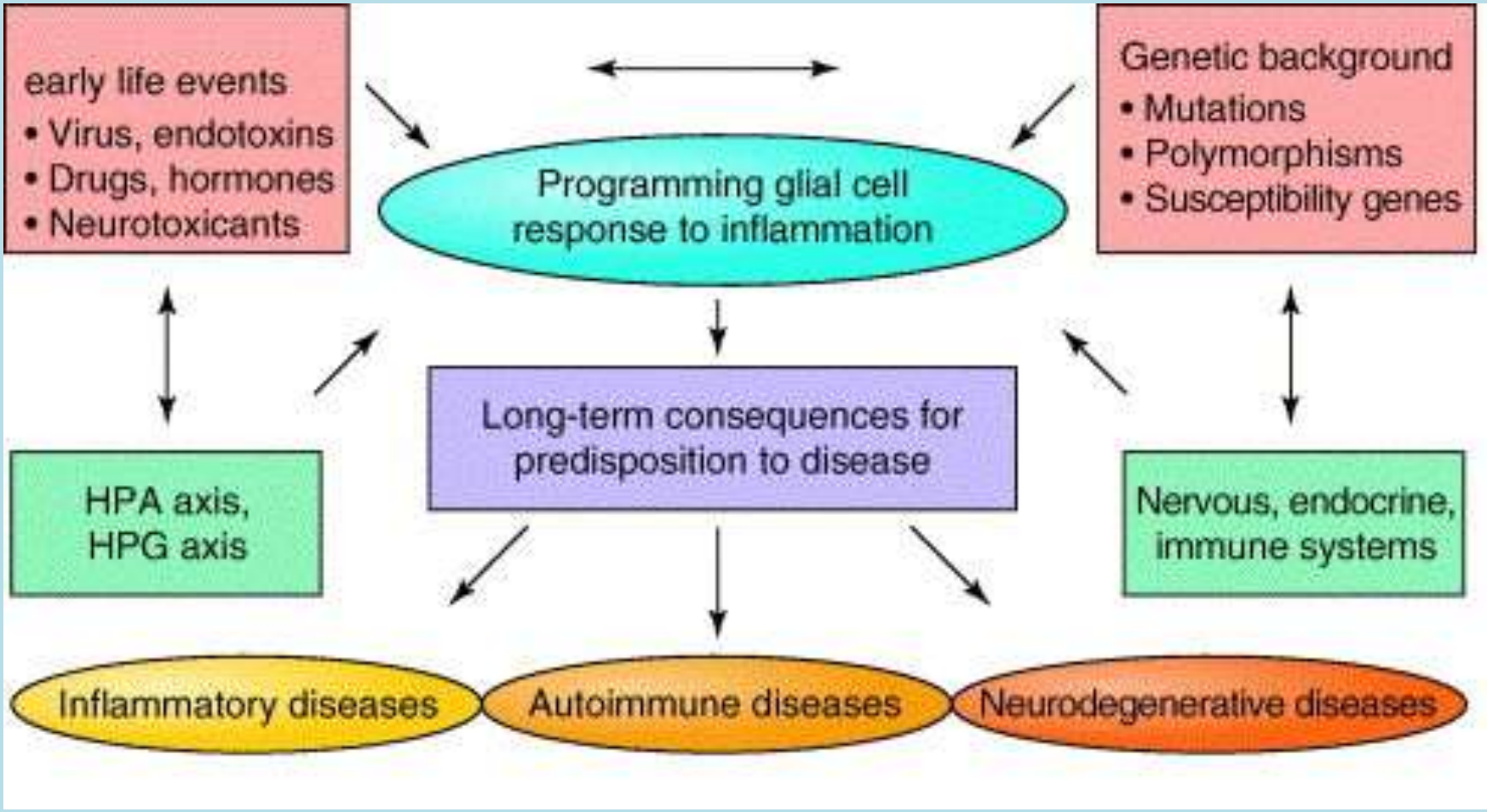
Willem de Kooning

The Dutch artist painted until he died at 93, even as he faced the slow loss of the mental power that made him a master of abstract expressionism

MARY ELLEN MARK



SIDE BY SIDE The effects of cell death in an Alzheimer's brain, left, are as dramatic as they look



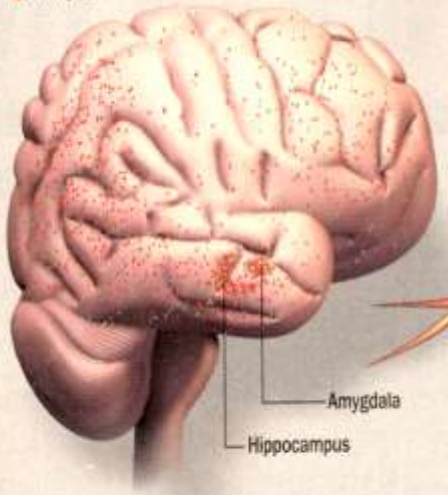
The impact of perinatal genetic, hormonal and environmental interactions on the inflammatory glial cell response and individual resistance or susceptibility to inflammatory diseases.

HOW ALZHEIMER'S DISEASE DEVELOPS IN THE BRAIN ...

Scientists can't yet say definitively what causes Alzheimer's disease, but any explanation has to account for the presence of sticky plaques outside the neurons and stringy tangles within them. Do the lesions occur simultaneously? Or, more likely, does one precede the other? Does something else trigger them both? Here's what's known so far:

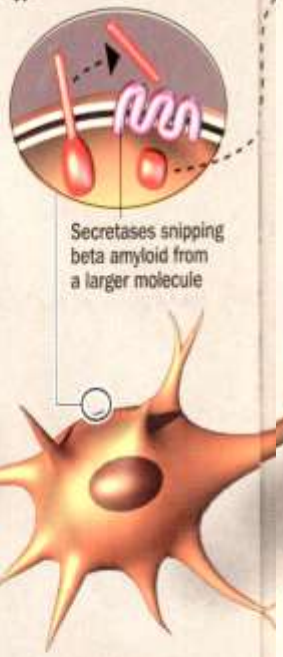
Tangles

Plaques



BETA AMYLOID

- **Even healthy cells use enzymes called secretases on their surface to make a protein called beta amyloid. But people with familial Alzheimer's produce too much amyloid, particularly one very sticky type**



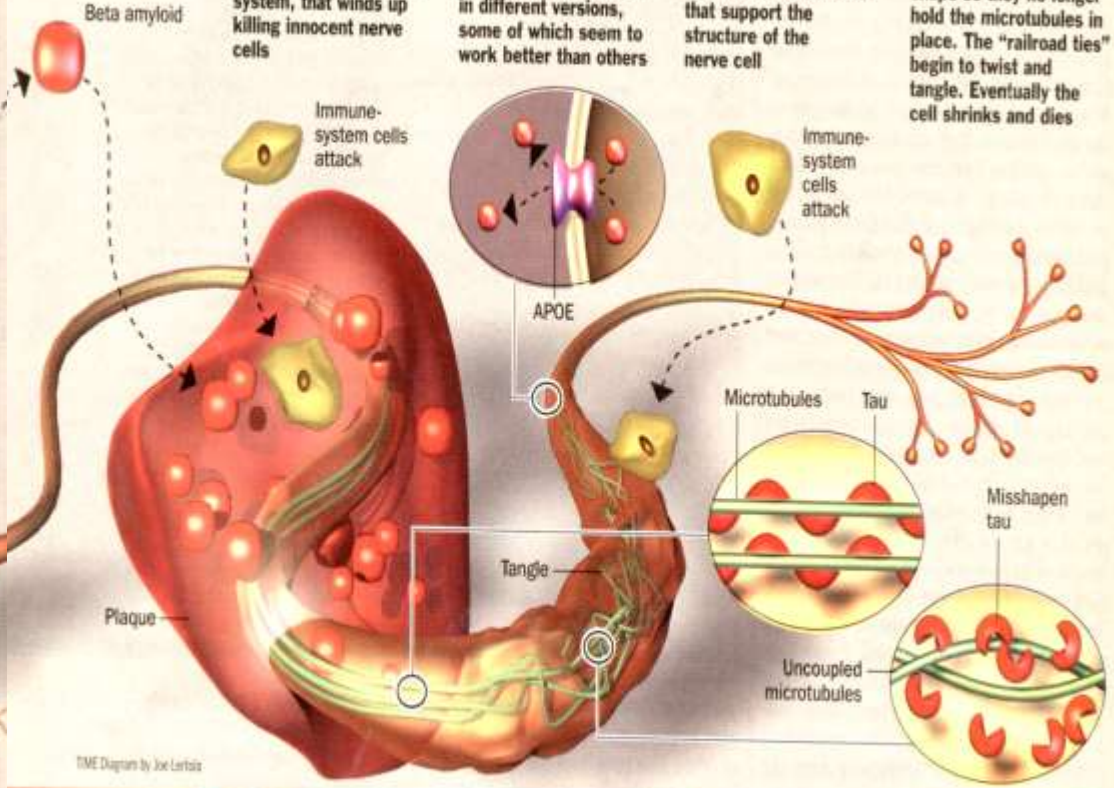
- **Beta amyloid forms plaques on the outside of brain cells**
- **The plaques grow so dense that they trigger an inflammatory reaction from the brain's immune system, that winds up killing innocent nerve cells**

APOE

- **Another molecule that may play a role in clearing amyloid plaques, APOE, comes in different versions, some of which seem to work better than others**

TAU

- **A molecule that acts much like the ties on a railroad track, tau assembles microtubules that support the structure of the nerve cell**
- **Chemical changes in the nerve cell cause the tau molecules to change shape so they no longer hold the microtubules in place. The "railroad ties" begin to twist and tangle. Eventually the cell shrinks and dies**



... AND HOW ITS PROGRESSION MAY BE STOPPED

BETA AMYLOID

- **Secretase inhibitors that theoretically should block the production of amyloid**

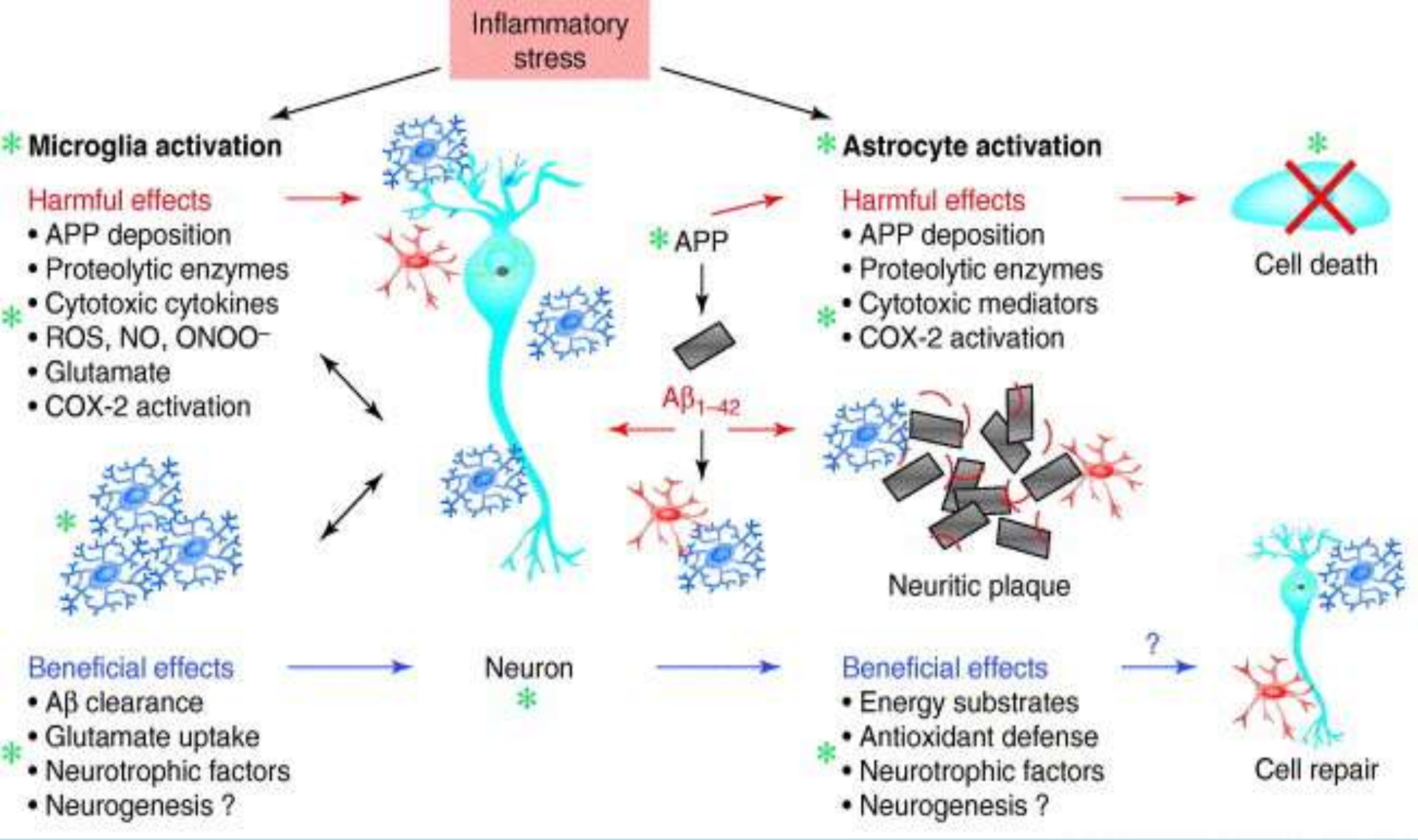
rotein are undergoing reliminary tests in uman volunteers

APOE

- **As scientists learn more about how APOE affects the formation of plaques, and possibly even tangles, they hope to identify new targets for drug development**

TAU

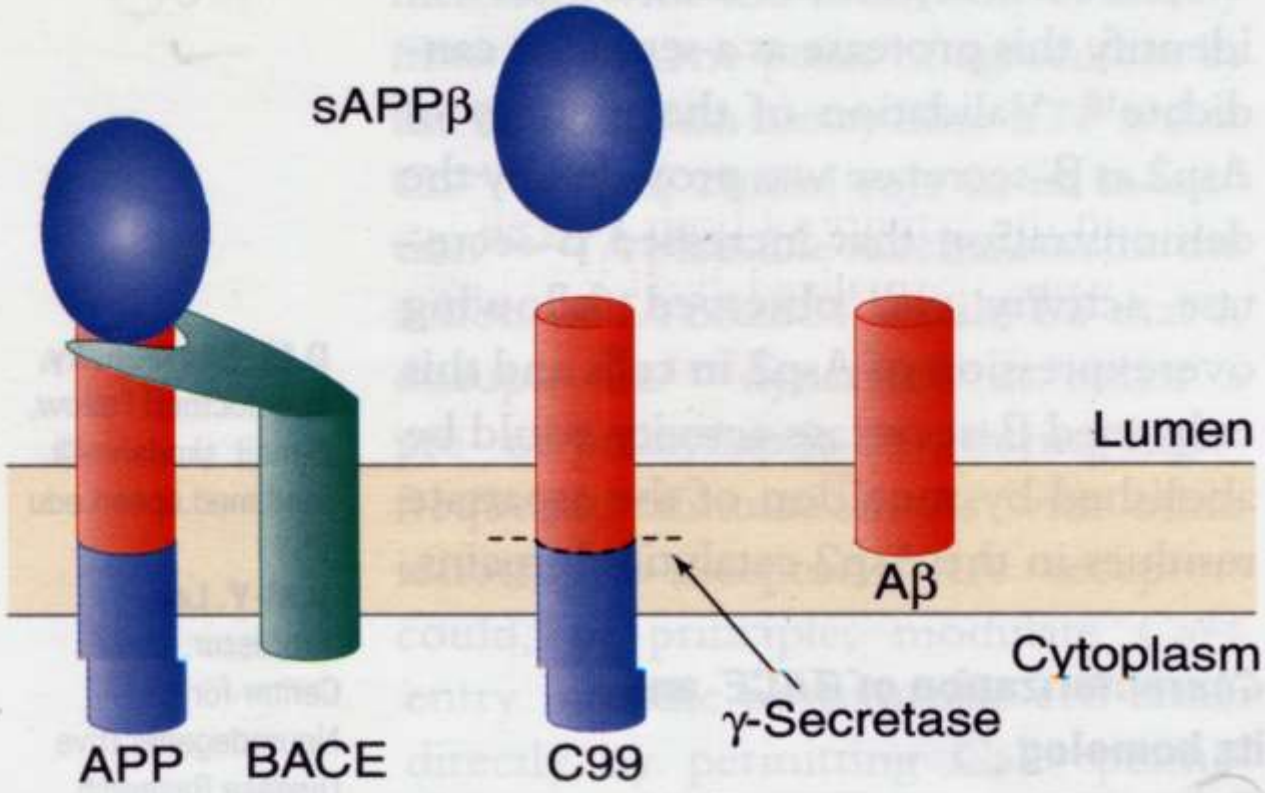
- **If researchers can develop compounds that allow tau to maintain its normal function, they may prevent neuronal tangles and subsequent cell death**



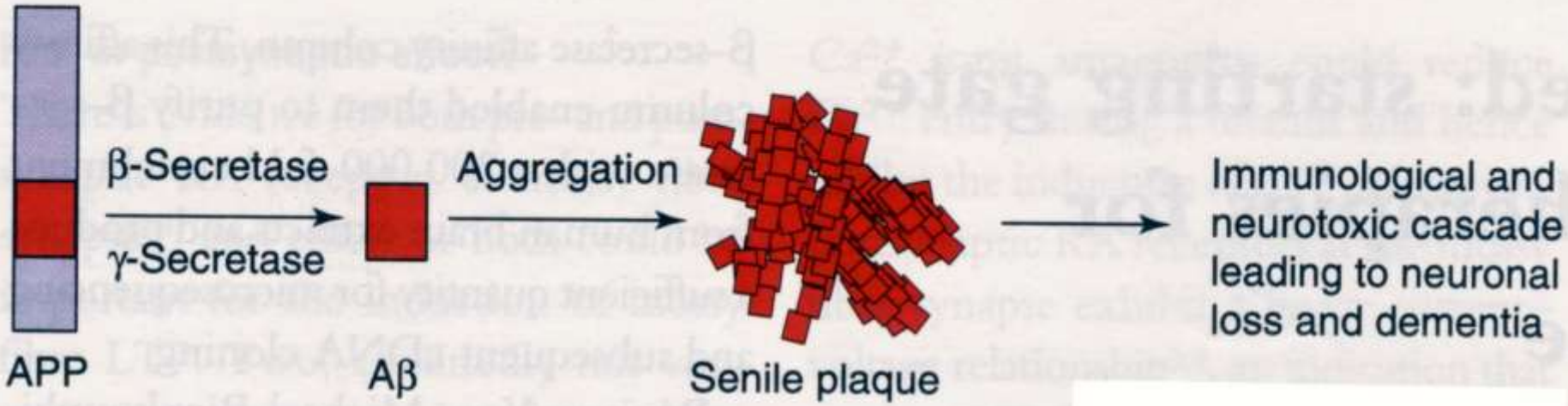
The detrimental and beneficial inflammatory pathways in Alzheimer's disease (AD) and potential pharmacological targets (*). A central event in the brains of AD patients is the deposition of the neurotoxic β-amyloid protein (Aβ1–42) from the amyloid precursor protein (APP), leading to the formation of neuritic plaques

ALZHEIMER'S DISEASE(AD)

- Alzheimer's disease is biggest unmet need in neurology
- > 12 million AD sufferers globally
- Majority of dementias after the age of 60 are due to AD
- Global decline of cognitive function progresses slowly- leaves end stage patient bedridden, incontinent under custodial care and death occurring 9 years after diagnosis



Cleavage of amyloid precursor protein (APP) by β-site APP cleaving enzyme (BACE) and γ-secretase. BACE and APP are both single-pass transmembrane proteins with short cytoplasmic domains. BACE cleaves APP in the lumen of the endoplasmic reticulum, Golgi network or endosome. This cleavage releases the soluble ectodomain of APP (sAPPβ) and the 99 amino acids at the carboxyl terminal of APP (C99). C99 is then cleaved by γ-secretase to release β-amyloid (Aβ). The identity of the enzyme responsible for γ-secretase cleavage is not known.



Production of β-amyloid (Aβ) and the pathogenesis of Alzheimer's disease (AD). Cleavage of the amyloid precursor protein (APP) by β- and γ-secretases generates Aβ , which can aggregate in the brain to produce senile plaques in AD. Senile plaques can then initiate a poorly understood pathological cascade that results in neuronal loss and dementia. Mutations in the genes that encode APP, presenilin 1 or presenilin 2 increase the production of Aβ from APP and cause an early-onset form of AD.

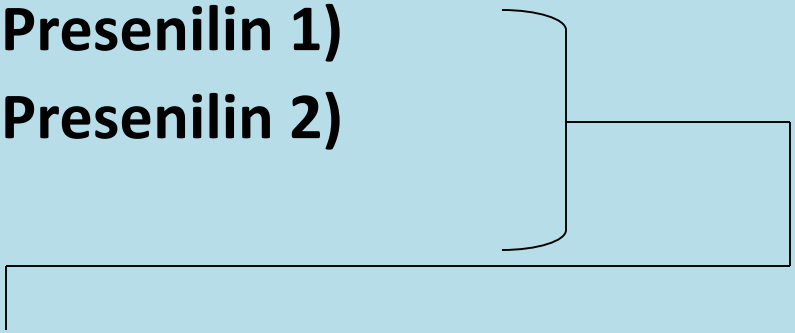
GENES & AD

- **Autosomal Dominant Familial AD(FAD) linked to mutations in 3 genes**

(a) APP (Encodes Amyloid Precussor Protein)

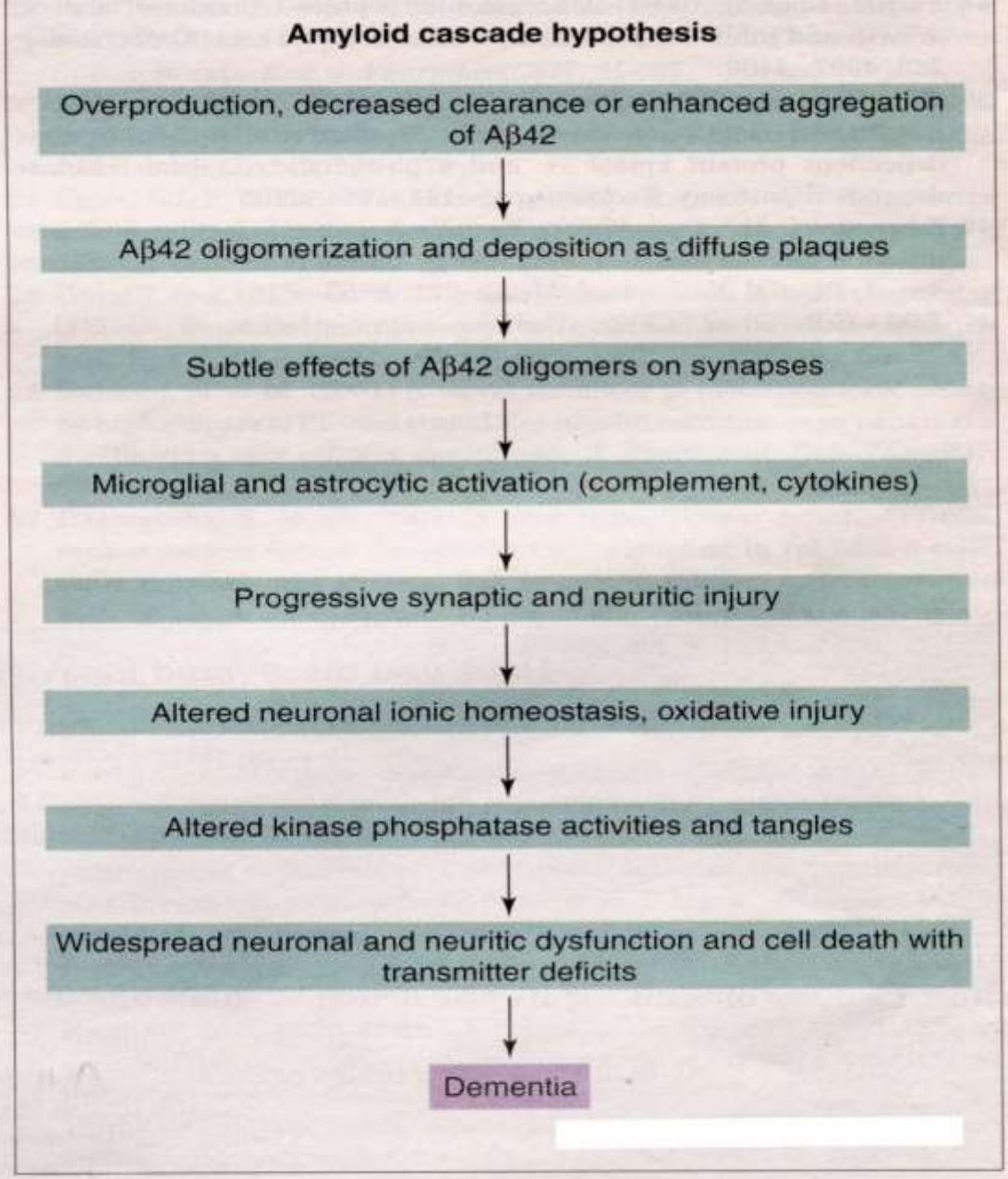
(b) PSEN 1 (Encodes Presenilin 1)

(c) PSEN 2 (Encodes Presenilin 2)

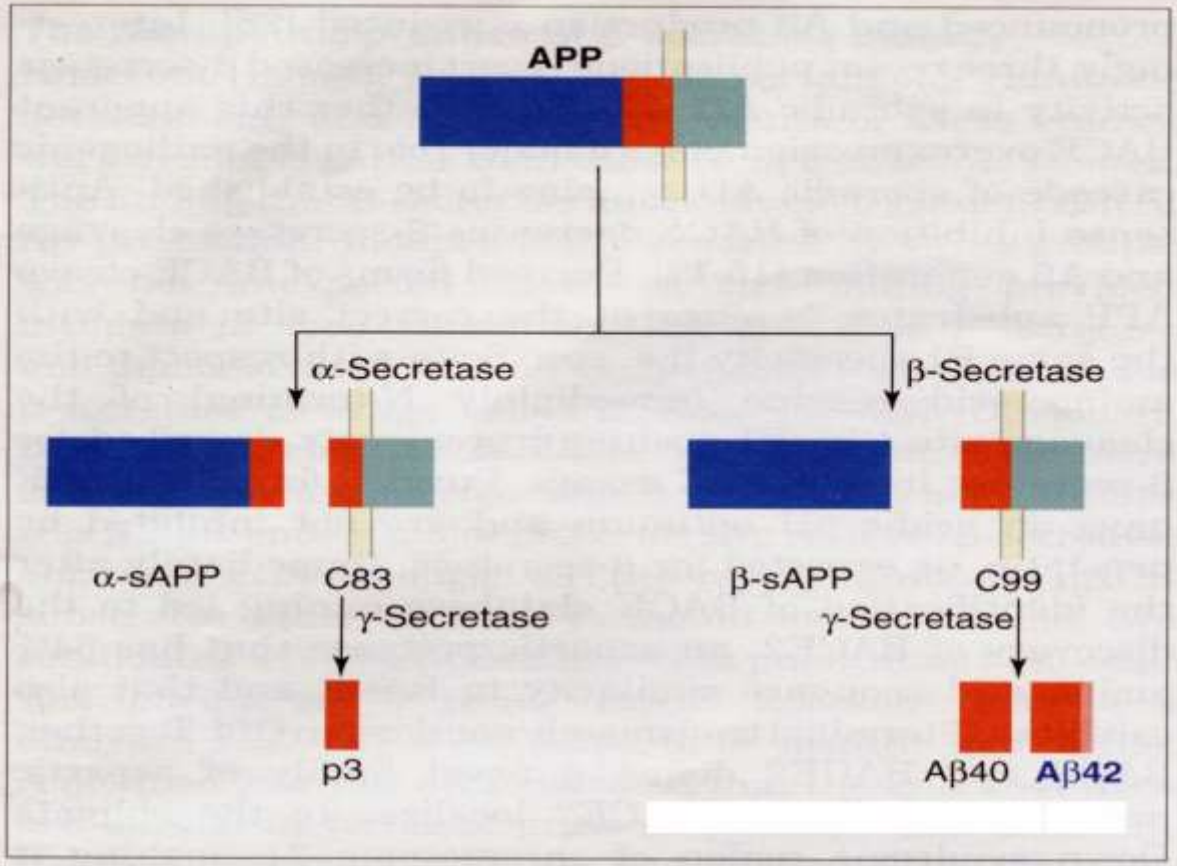


Components of gamma secretase complex

- **FAD linked mutations of PSEN 1, PSEN 2 & APP result in increased production of Aβ 42- More amyloidogenic than Aβ 40**



The amyloid cascade hypothesis . The sequence of pathogenic events leading to Alzheimer's disease (AD) is shown. The cascade is initiated when amyloid-β-42 (Aβ42) is generated. In familial early onset AD Aβ42 is overproduced as a result of pathogenic mutations. In sporadic AD various factors can contribute to an increased load of Aβ42 oligomers and aggregates.



Schematic of the amyloid precursor protein (APP) and its metabolites, relevant to Alzheimer's disease (AD) (not drawn to scale). The transmembrane protein APP (membrane indicated in yellow) can be processed along two major pathways, the α-secretase pathway and the amyloid-forming β-secretase pathway. In the α-secretase pathway, α-secretase cleaves in the middle of the β-amyloid (Aβ) region (red) to release a large soluble APP-fragment [α-sAPP (blue)]. The C-terminal C83 peptide is metabolized to p3 by γ-secretase. In the amyloid-forming β-secretase pathway, β-secretase releases a large soluble fragment [β-sAPP (blue)]. The C-terminal C99 peptide is then cleaved by γ-secretase at several positions, leading to the formation of Aβ40 and the pathogenic Aβ42. γ-Secretase cleavage also releases the APP intracellular domain [AICD (green)], which could play a role in transcriptional regulation . The effects of β- and γ-secretase inhibitors can be distinguished in secondary assays: both inhibitor classes block the formation of pathogenic Aβ42, but β-secretase inhibitors also block the formation of β-sAPP and C99, whereas γ-secretase inhibitors also block the formation of p3 and the AICD (green) and lead to accumulation of C99 and C83.

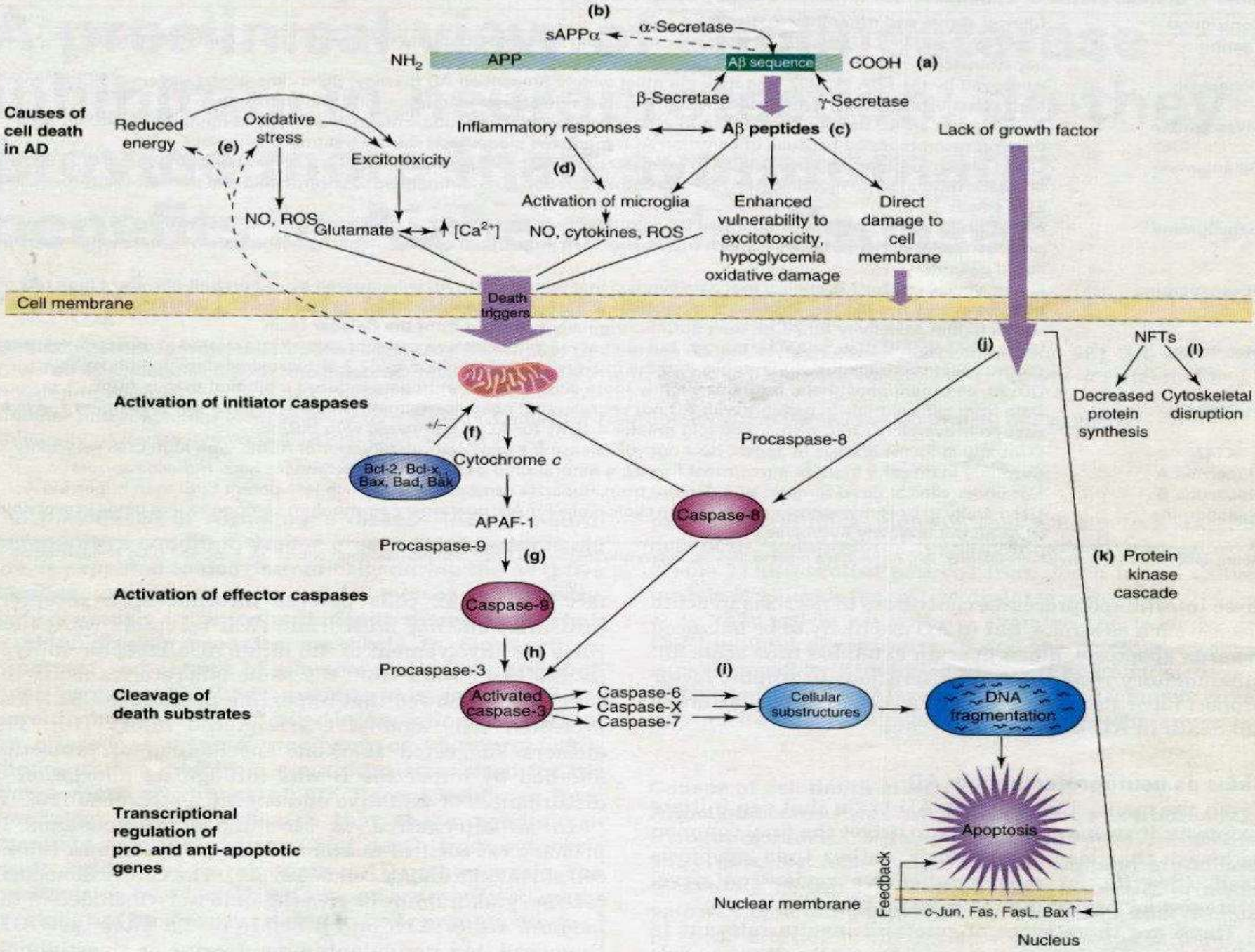
CAUSES OF CELL DEATH IN ALZHEIMER'S DISEASE

- Triggers that initiate apoptosis in AD are β amyloid (Aβ) containing plaques and neurofibrillary tangles (NFTS).
- NFTS are composed of paired helical filaments of aggregated hyperphosphorylated forms of microtubules associated with protein tau.
- Their presence causes reduction of cellular protein synthesizing capacity, loss of a functioning cytoskeleton and cell death. Other mechanisms of cell death are

(I) Excitotoxicity

(ii) Reduced energy metabolism and/or mitochondrial dysfunction

(iii) Free radical production and oxidative stress.


(b)
sAPPα
α-Secretase
NH2
APP
Aβ sequence
COOH
(a)
β-Secretase
γ-Secretase
Causes of cell death in AD
Reduced energy
(e)
Oxidative stress
Excitotoxicity
Inflammatory responses
Aβ peptides
(c)
Lack of growth factor
(d)
Activation of microglia
Enhanced vulnerability to excitotoxicity, hypoglycemia oxidative damage
Direct damage to cell membrane
NO, ROS
Glutamate
↑ [Ca2+]
NO, cytokines, ROS
Cell membrane
Death triggers
(j)
NFTs
(l)
Decreased protein synthesis
Cytoskeletal disruption
Activation of initiator caspases
+/−
(f)
Procaspase-8
Bcl-2, Bcl-xL, Bax, Bad, Bak
Cytochrome c
APAF-1
Caspase-8
Procaspase-9
(g)
(k) Protein kinase cascade
Activation of effector caspases
Caspase-9
(h)
Procaspase-3
(i)
Cleavage of death substrates
Activated caspase-3
Caspase-6
Caspase-X
Caspase-7
Cellular substructures
DNA fragmentation
Transcriptional regulation of pro- and anti-apoptotic genes
Apoptosis
Feedback
Nuclear membrane
c-Jun, Fas, FasL, Bax↑
Nucleus

CAUSES OF CELL DEATH IN ALZHEIMER'S DISEASE

Three processes contribute to necrosis (in stroke) or apoptosis (AD). Three types of cytotoxic insults relevant to cell death in AD are used widely in cell culture models to study neuroprotection

- **Oxygen and glucose deprivation**
- **Exogenous glutamate, and**
- **Aβ.**

CHEIs are neuroprotective in all these models.

ALZHEIMER'S DISEASE

There is significant dysfunction of basal forebrain ACh system. Treatment of patients with Alzheimer's disease rests on the strategy of enhancing acetylcholine (ACh) – mediated transmission.

Cholinesterase inhibitors have been used. Therapeutic benefit is likely to be more complex than simply replacement of lost ACh. The CHE-inhibitors include tacrine, donepezil, galantamine, granstigmine and huperzine A.

PROTECTION AGAINSTS OGD DEPRIVATION

Experiments on pheochromocytoma cell lines (PC12 cells) – exposure to OGD – oxidative stress showed increased SOD and increased concentration of malondialdehyde with loss of neurites and cell death.

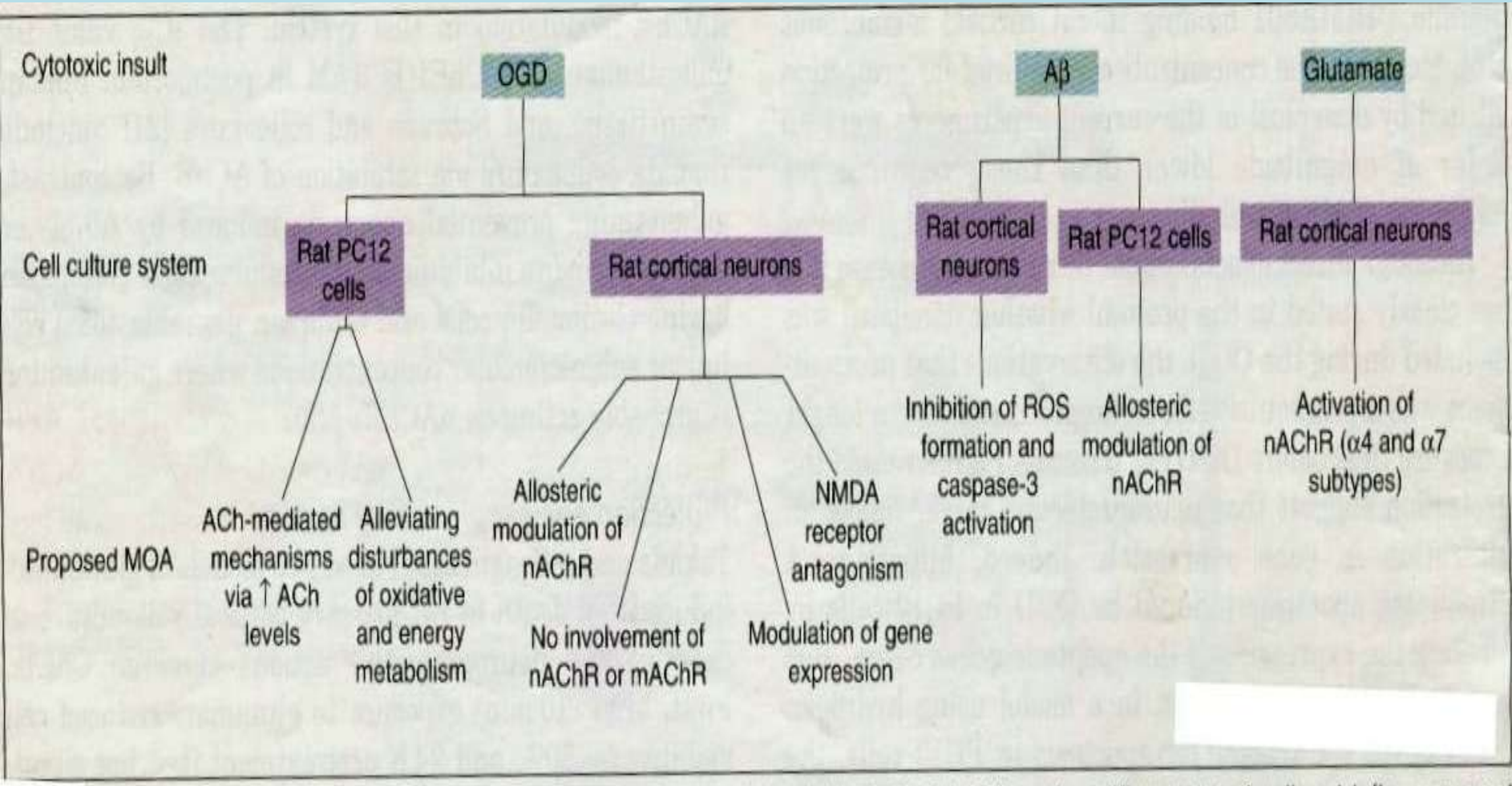
Pre treatment with huperzine or donepezil for 2h before OGD reversed all these changes in a concentration dependent manner in another model – *in vitro* model of ischemia in rat cortical neurons.

OGD for 40-50 min caused cell shrinkage and /or cell death. Donepezil introduced before the OGD reversed both cell shrinkage and cell death.

PROTECTION AGAINSTS OGD DEPRIVATION

Concentrations of donepezil were in the same range as those achieved clinically (0.1 – 10 μm). Huperzine A attenuated apoptosis induced by OGD in PC12 cells by altering the expression of apoptotic genes c - jun, Bax and Bcl-2 . Proapoptic gene *p53* was also attenuated by tacrine and huperzine.

Thus CHEIs modulate gene expression. Other studies have shown that donepezil can act independently of the inhibition – perhaps binding to allosteric site on CHE, downregulating it.



Proposed mechanisms of action for the neuroprotective effects of cholinesterase inhibitors (ChEIs). Evidence from different cytotoxic cell models [i.e. oxygen and glucose deprivation (OGD) or β-amyloid (Aβ) toxicity in rat PC12 cells and rat cortical neurons, and glutamate toxicity in rat cortical neurons] suggests that ChEIs can mediate their neuroprotective properties through several different mechanisms. Abbreviations: ACh, acetylcholine; mAChR, muscarinic acetylcholine receptor; MOA, mechanism of action; NMDA, N-methyl-D-aspartate; nAChR, nicotinic acetylcholine receptor; rat PC12 cells, rat pheochromocytoma cell line; ROS, reactive oxygen species.

PROTECTION AGAINST GLUTAMATE TOXICITY

Donepezil, tacrine, galantamine, neostigmine, pyridostigmine or metrifonate were the most neuroprotective in glutamate induced cell death in rat primary cortical cell culture.

Donepezil produced concentration related protection – the protective effect of donepezil was blocked by mecamylamine, but not scopolomine, suggesting nAChr mediated action (both α4 and α7 nAChrs). A caspase inhibitory action was also observed.

PROTECTION AGAINST β-AMYLOID TOXICITY

Tacrine, donepezil, huperzine A and ganstigmine protect against toxicity induced by Aβ.

Inhibition of reactive oxygen species and caspase – 3 have been suggested as the mechanism.

LONG LASTING COGNITIVE IMPROVEMENT WITH NICOTINIC RECEPTOR AGONISTS

Agonists of nicotinic acetylcholine receptors (nAChRs) produce long lasting cognitive effects in animal models and humans. The duration of these congnitive effects can outlast the presence of agonists in the system and the persistence of cognitive enhancement is increased further by repeated exposure.

LONG LASTING COGNITIVE IMPROVEMENT WITH NICOTINIC RECEPTOR AGONISTS

Cognitive enhancement outlasts the presence of compounds in the blood. Receptor occupancy returns to normal within two hours. No active metabolites can be identified.

Mechanisms of Synaptic Plasticity And Long Term Enhancement of Memory:
Increase in the number of synaptic connections. Efficiency of synaptic connections between neurons.

LONG TERM MOLECULAR CHANGES:

Activation of nAChRs of the α7 and α4b2 have been studied in several cell systems and overlap with molecular systems of memory .

A cascade of cellular signals is initiated – influx of Ca^{2+} and other cations, produces sufficient depolarization to activate voltage gated Ca^{2+} channels – neurotransmitter release stimulated directly & indirectly via activation of protein kinase C – second messenger systems such as Ca^{2+} calmodulin – dependent kinase and MAPK (Mitogen – Activated Protein Kinase) and the long lasting phosphorylation of CREB (cAMP response element binding protein-1) in the nucleus..

LONG TERM MOLECULAR CHANGES:

In turn phosphorylated CREB increases the expression of the early immediate gene c-fus and junB in brain areas such as striatum, cortex, amygdala, superior colliculus and monoamine containing nuclei.

These effects can be long lasting. Numerous genes- those involved in intracellur signaling, transcription, translation, protein modification and neuro-transmission are affected.

LONG TERM MOLECULAR CHANGES:

Expression of gene that encodes tyrosine hydroxylase (TH) which catalyses rate limiting step in the synthesis of NA & DA is stimulated by nAChRs.

Both acute and chronic administration of nicotine increase the activity in hippocampus which persists for several weeks after nicotine treatment is discontinued.

There is long lasting release of NA in hippocampus and dopamine in nucleus acumbens when there is no nicotine in plasma.

AD & β- Secretase

- β - Secretase was identified as the transmemberane aspartic protease BACE
- BACE & its homologue BACE 2 New branch of Pepsin family
- Inhibitors of β-Secretase

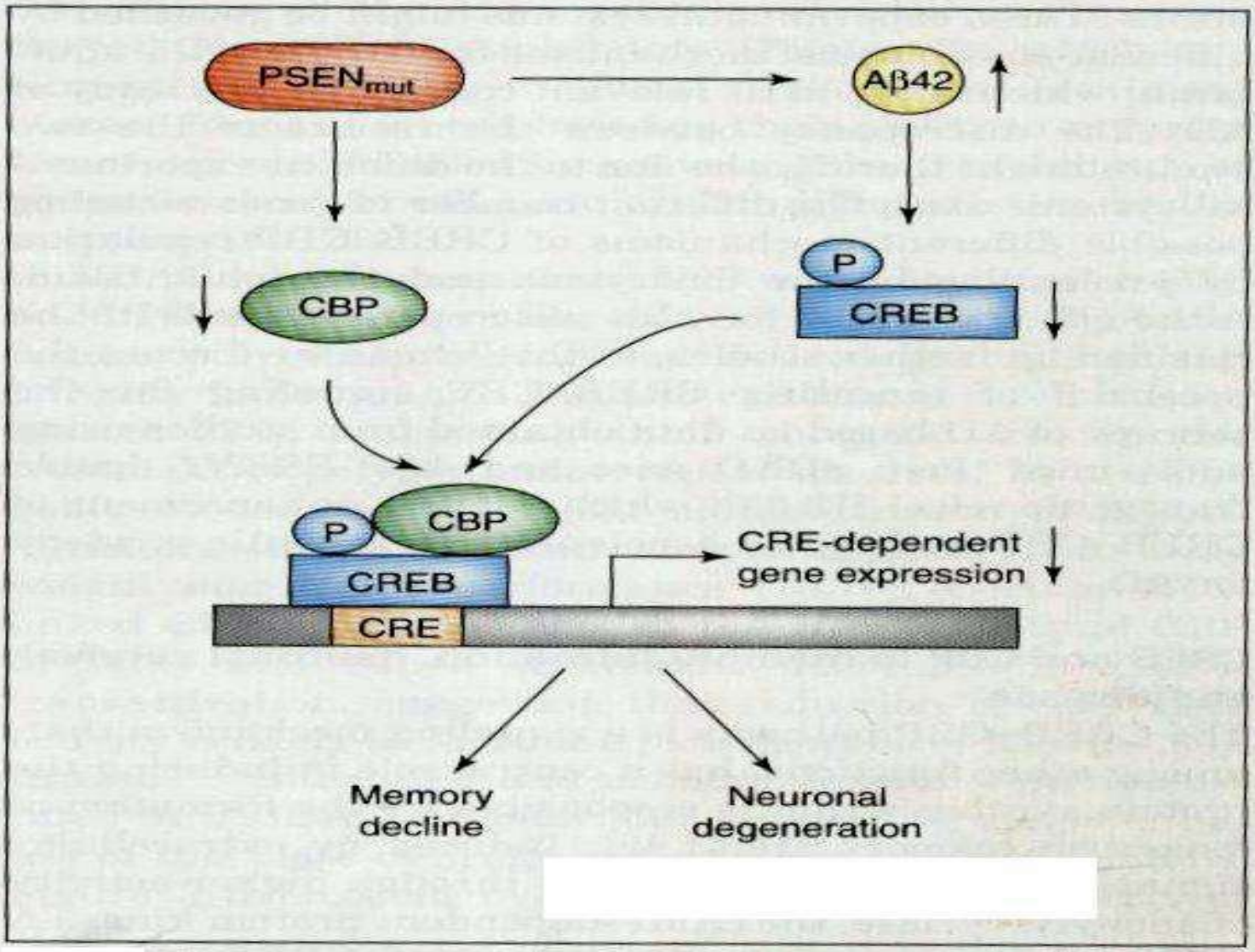
(a) Small molecules more desirable. Penetrability to CNS better.

(b) High Throughput Screening of compound collections

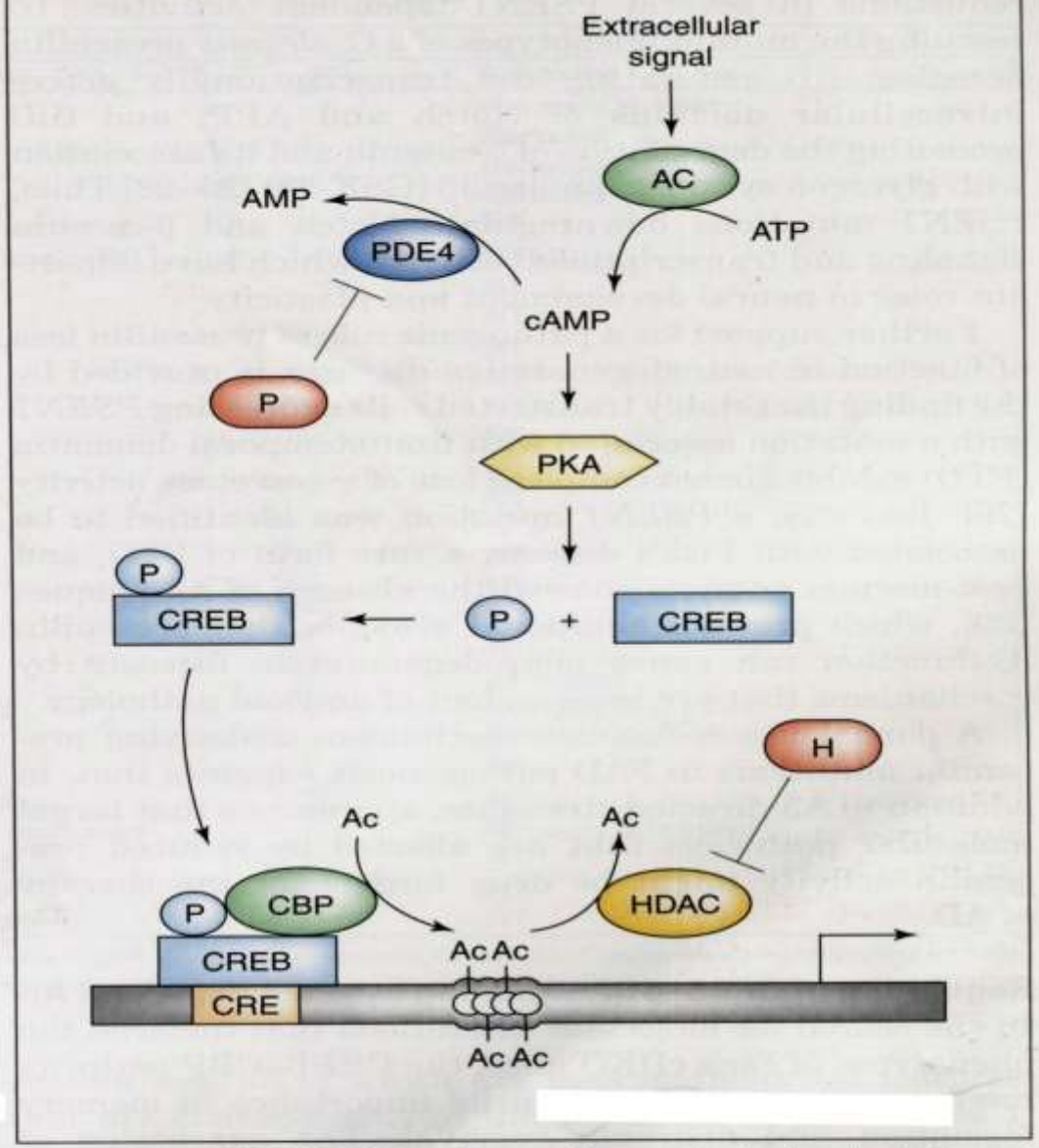
(c) Natural plant extracts have been used exclusive specificity for BACE

PSEN GENES & FAD

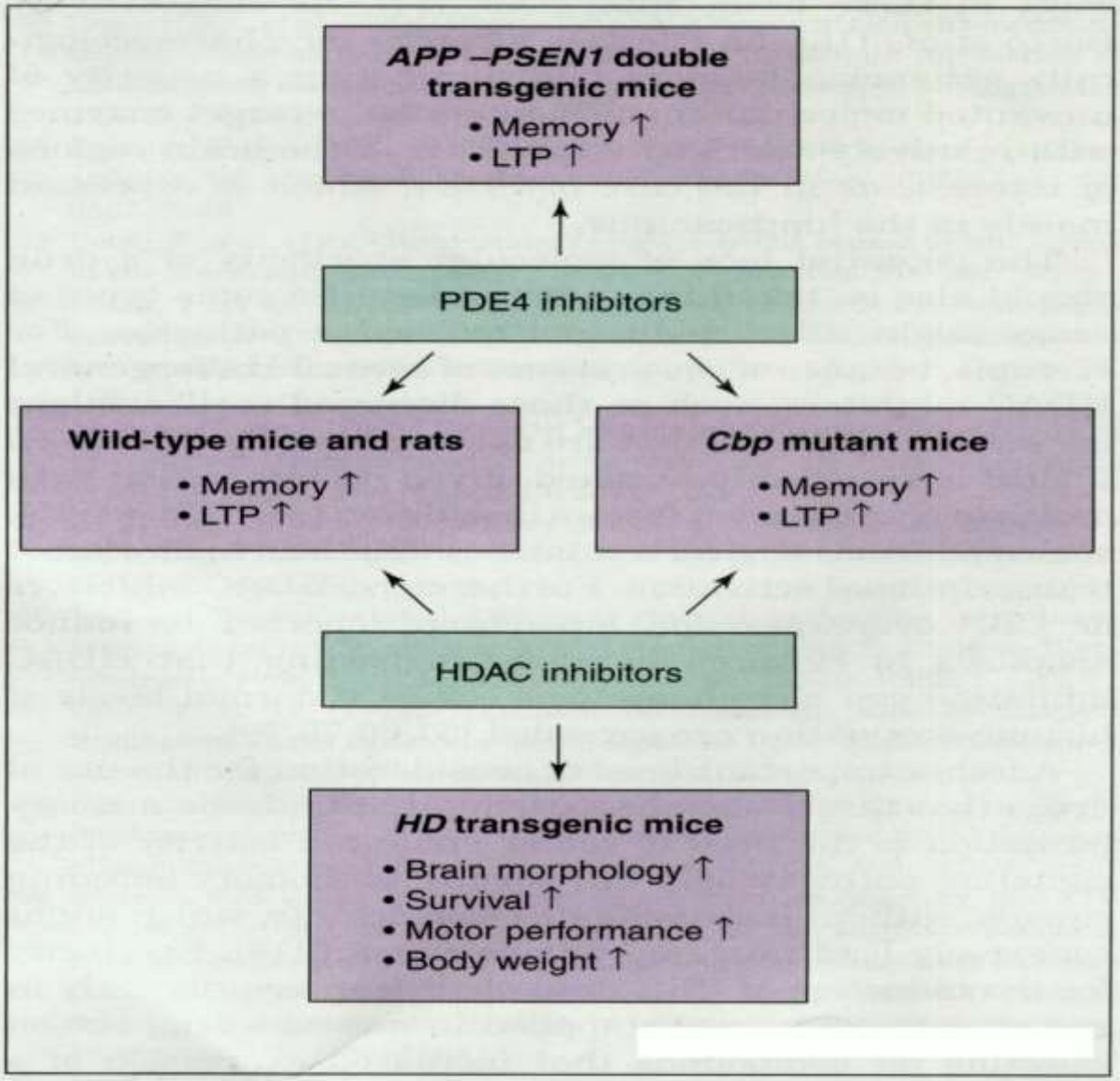
- **Mutations in PSEN genes are the major cause of FAD**
- **Mutations in PSEN2 leads to severe impairments(PSEN1 related mutations mild impairments)**
- **PSEN CDKO mice exhibit deficits in Hippocampal Spatial and associative memory with impairment of synaptic plasticity (resemblance to human AD)**
- **With advancing age synaptic, dendritic and neuro degeneration, marked inflammatory responses and hyperphosphorylation of cytoskeletal protein TAU – All features characteristic of AD brain**



Proposed model of the downregulation of CREB–CBP signaling by FAD-linked presenilin mutations. CRE-dependent gene expression is controlled by the phosphorylated (P) form of the transcription factor CREB and the coactivator CBP. FAD-linked presenilin mutations result in increased Aβ42 production, which leads to decreased CREB phosphorylation. Reduced presenilin activity, probably conferred by FAD-linked mutations, leads to a decrease in CBP expression. Downregulation of CRE-dependent gene expression caused by either or both mechanisms results in memory decline and neuronal degeneration.



The cAMP–CREB–CBP pathway and its targeting by phosphodiesterase 4 (PDE4) inhibitors and histone deacetylase (HDAC) inhibitors. Extracellular signals activate adenylyl cyclase (AC), which catalyzes the synthesis of cAMP, which in turn induces phosphorylation of CREB by protein kinase A (PKA). Phospo-CREB binds to CBP and activates transcription of genes containing the CRE sequence in their promoters. CBP also activates transcription by acetylating histones. PDE4 inhibitors (P) (red) increase the concentration of cAMP by inhibiting its hydrolysis into AMP. HDAC inhibitors (H) (red) increase histone acetylation status by inhibiting histone deacetylation. Abbreviation: Ac, acetyl group.



Positive effects of phosphodiesterase 4 (PDE4) inhibitors and histone deacetylase (HDAC) inhibitors on nervous system-dependent phenotypes of rodent models. PDE4 inhibitors and HDAC inhibitors enhance memory and long-term potentiation (LTP) in wild-type mice and rats and ameliorate memory and LTP deficits in heterozygous *Cbp* mutant mice. PDE4 inhibitors also improve impaired memory and LTP in *APP–PSEN1* double transgenic mice. HDAC inhibitors improve brain morphology, survival, motor performance and body weight in a transgenic mouse model of HD.

PSEN & MEMORY

- **PSENs positively regulate the trnscription of cAMP Response Element (CRE)- containing genes, some of which are important for memory formation and neural survival.**

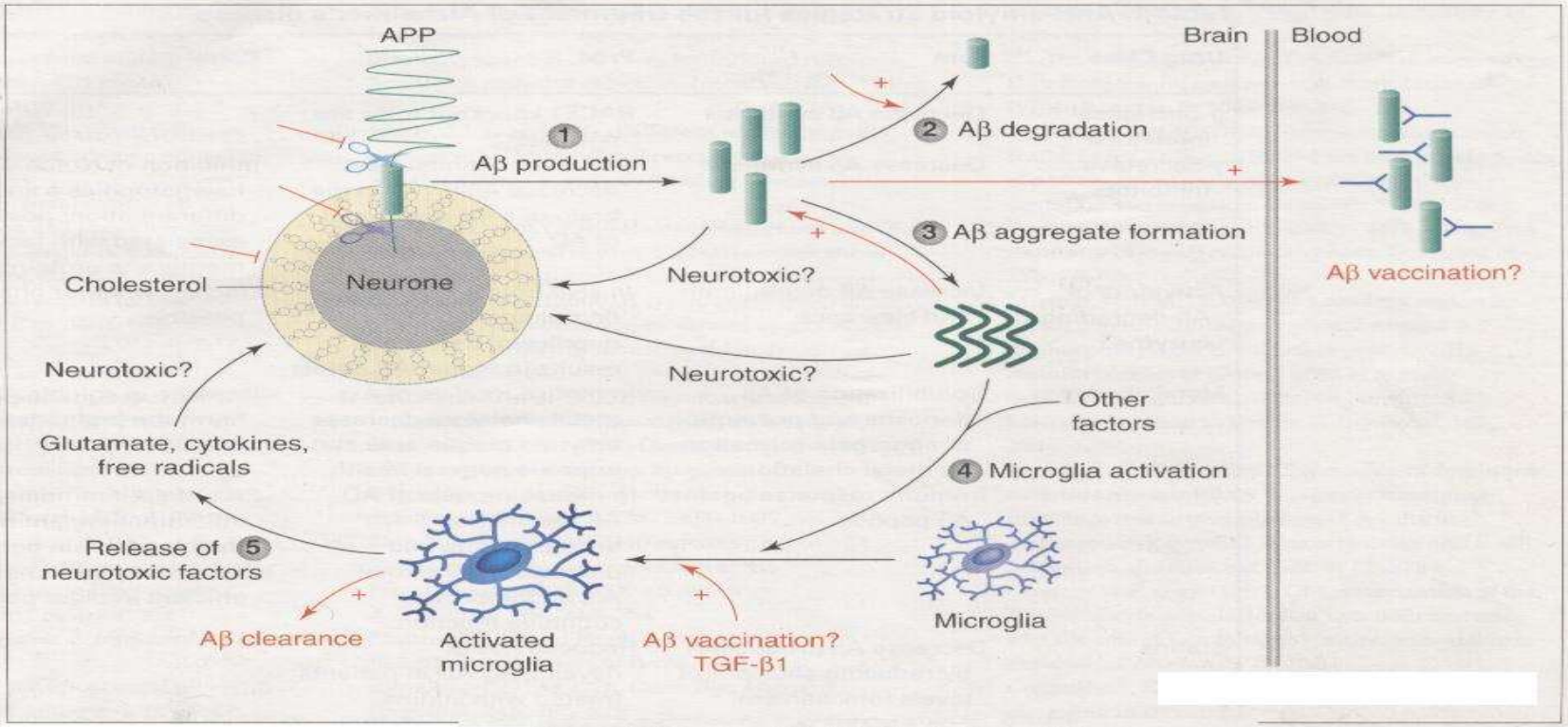
- **PDE4 and histone decacetylase inhibitors which can enhance CRE dependent gene expression can ameliorate memory deficits and neurodegeneration in animal models.**

- **Modulation of CRE dependent transcription might be beneficial for the treatment of dementia in AD**

Table Anti-amyloid strategies for the treatment of Alzheimer's disease[a]

Drug Class	Aim	Pros	Cons
β-Secretase inhibitors	Decrease Aβ synthesis	BACE1 knockout mice are normal	?
γ-Secretase inhibitors	Decrease Aβ synthesis	γ-Secretase inhibitors decrease Aβ levels in the brain of a mouse model of AD	Inhibition of Notch signalling could affect haematopoiesis and lymphocyte differentiation; possible side-effects associated with lack of cleavage of other membrane proteins
Activators of Aβ-degrading enzymes	Increase Aβ degradation and clearance	*In vivo* (mice) demonstration that neprilysin[b] deficiency results in higher Aβ levels	Unclear whether pharmacologically possible
Metal chelators	Solubilization of Aβ deposits and prevention of aggregate formation by metal chelation	In mouse models of AD metal chelators decrease amyloid plaque area and improve general health	Increase in soluble Aβ could potentially harm the brain; deficiency in vitamin B12, and SMON
Aβ vaccination	Immune response against Aβ peptide	In mouse models of AD Aβ vaccination decreases amyloid plaque area and total Aβ, and improves cognitive function	Risk of autoimmunity and brain inflammation; antibodies might not cross the blood–brain barrier in humans as they do in mice; immune response might not be efficient in older people
Statins	Decrease Aβ production by reducing cholesterol levels (mechanism remains unknown)	Reduced risk of developing AD in patients treated with statins; statins reduce cerebral Aβ load in guinea-pigs and mice	?
NSAIDs	Decrease inflammation in the brain that contributes to neuronal loss; inhibition of $A\beta_{1-42}$ generation	Reduced risk of developing AD in patients treated with NSAIDs	Side-effects, mostly at the level of the gastrointestinal tract following prolonged treatment

[a]Abbreviations: Aβ, β-amyloid; AD, Alzheimer's disease; BACE1, β-site APP-cleaving enzyme 1; NSAIDs, non-steroidal anti-inflammatory drugs; SMON, subacute myelo-optic neuropathy.
[b]Neprilysin (neutral endopeptidase) is a metallopeptidase that has been shown to degrade Aβ.



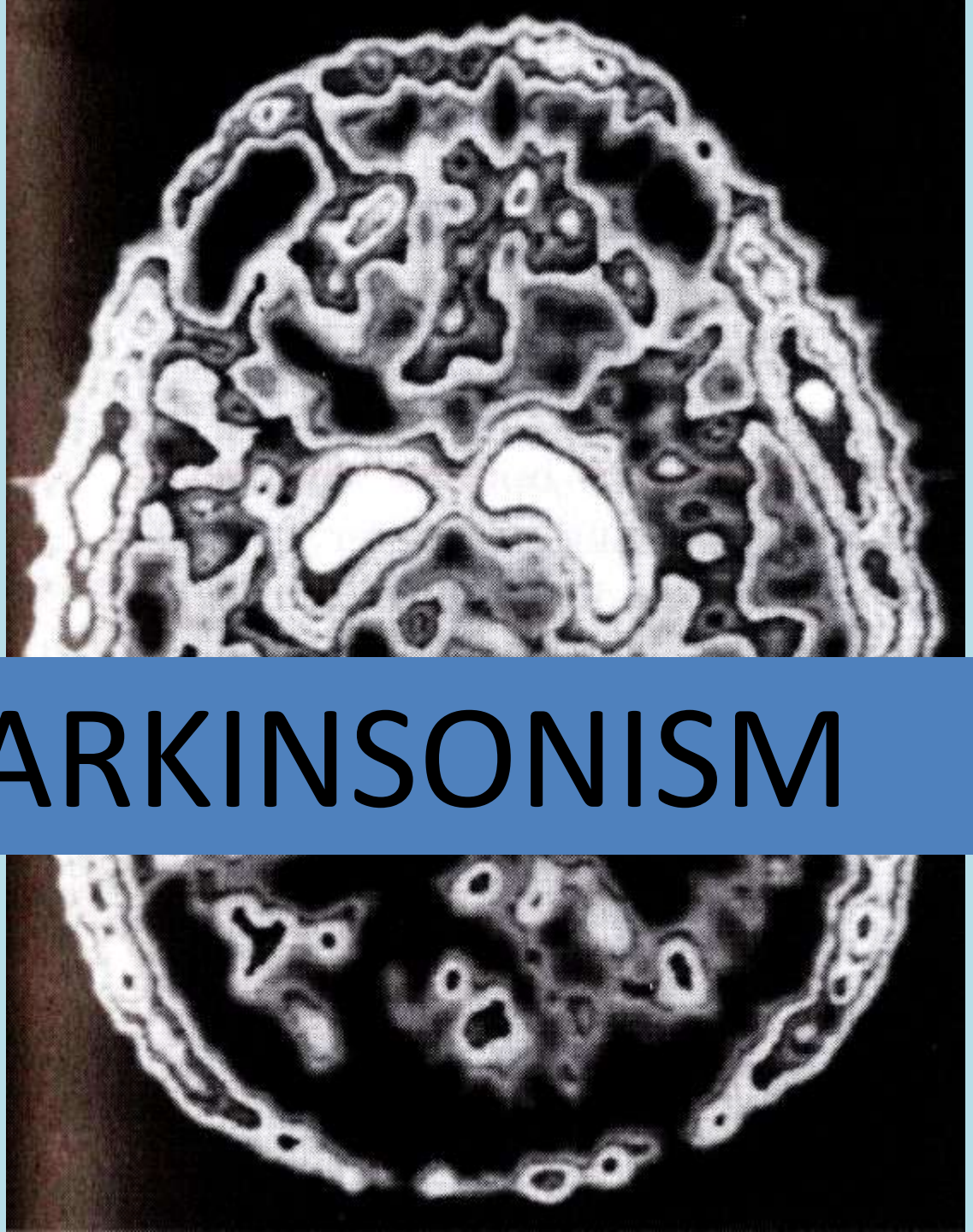
The amyloid hypothesis in Alzheimer's disease (AD) and candidate targets for therapeutic intervention. AD is characterized by two types of protein aggregates, neurofibrillary tangles and β-amyloid (Aβ) plaques, distributed in regions of the CNS involved in learning and memory. Soluble Aβ (green cylinders) is formed following the cleavage of Aβ precursor protein (APP) by enzymatic activities known as β-secretase (purple scissors) and γ-secretase (cyan scissors) (1). Aβ formed is then degraded by enzymes (2). The balance between Aβ production and degradation can be disrupted leading to Aβ accumulation beyond pathological levels and, in turn, increased levels of Aβ aggregates (3; green) and deposits in the brain. Aggregates and Aβ fibrils could themselves be neurotoxic or could activate microglia (4), which can release neurotoxic factors as part of an inflammatory response (5). Several steps could be targeted pharmacologically to treat AD (indicated by red arrows). For example, inhibitors of β-secretase and γ-secretase or cholesterol-lowering drugs (blunt arrows) could be used to decrease the production of Aβ. It is possible that activators of Aβ-degrading enzymes could be developed to reduce Aβ levels and metal chelators could be used to dissolve amyloid plaques. Furthermore, Aβ vaccination is proposed to sequester Aβ in the blood, which in turn would induce a rapid efflux of Aβ from the brain. Microglia can also be activated by Aβ vaccination or by transforming growth factor β1 (TGF-β1), leading to increased Aβ clearance and neuroprotection.

Conclusions :

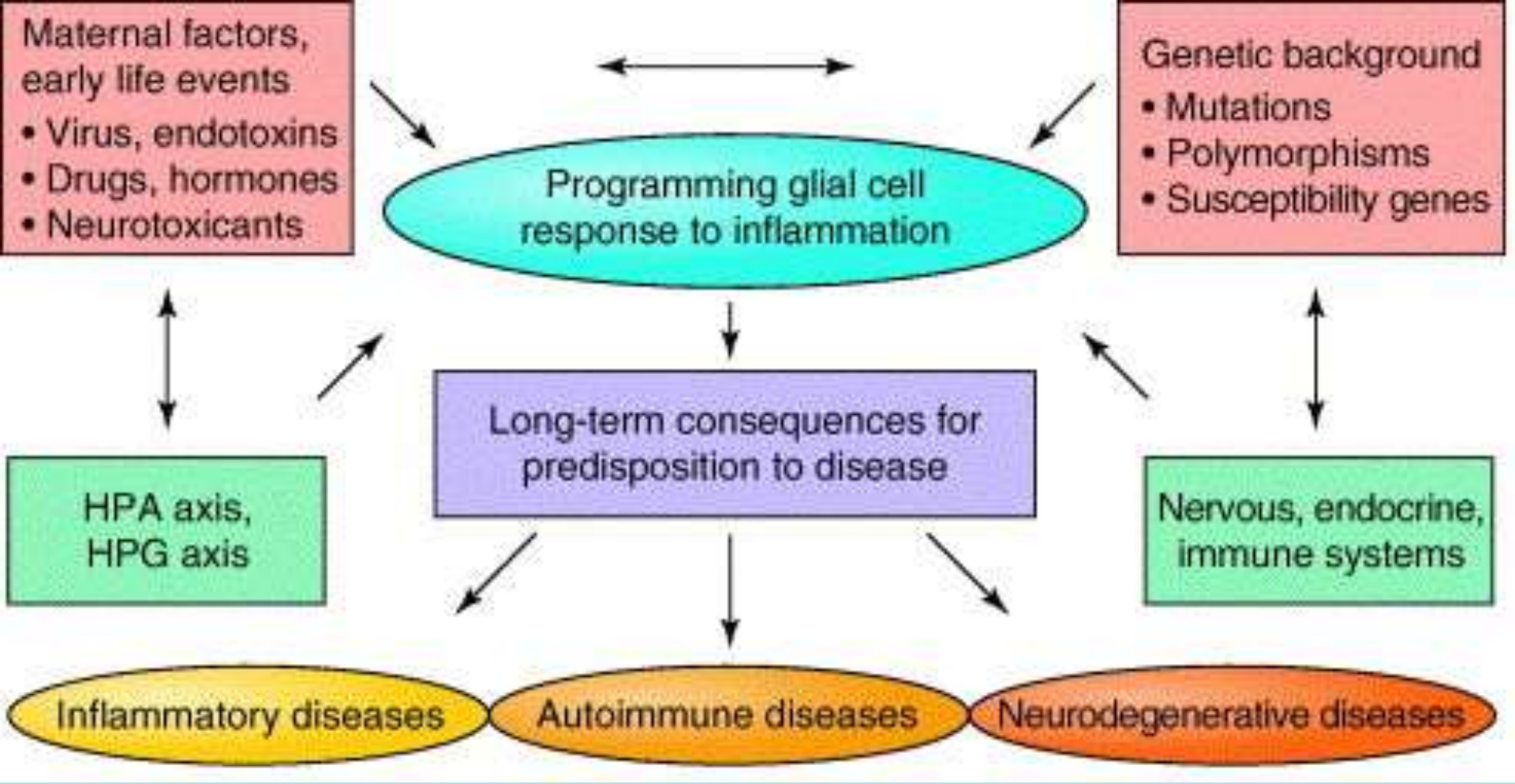
No cure for AD is presently available.

ACHEI provide symptomatic relief through ACHE inhibition and other mechanisms.

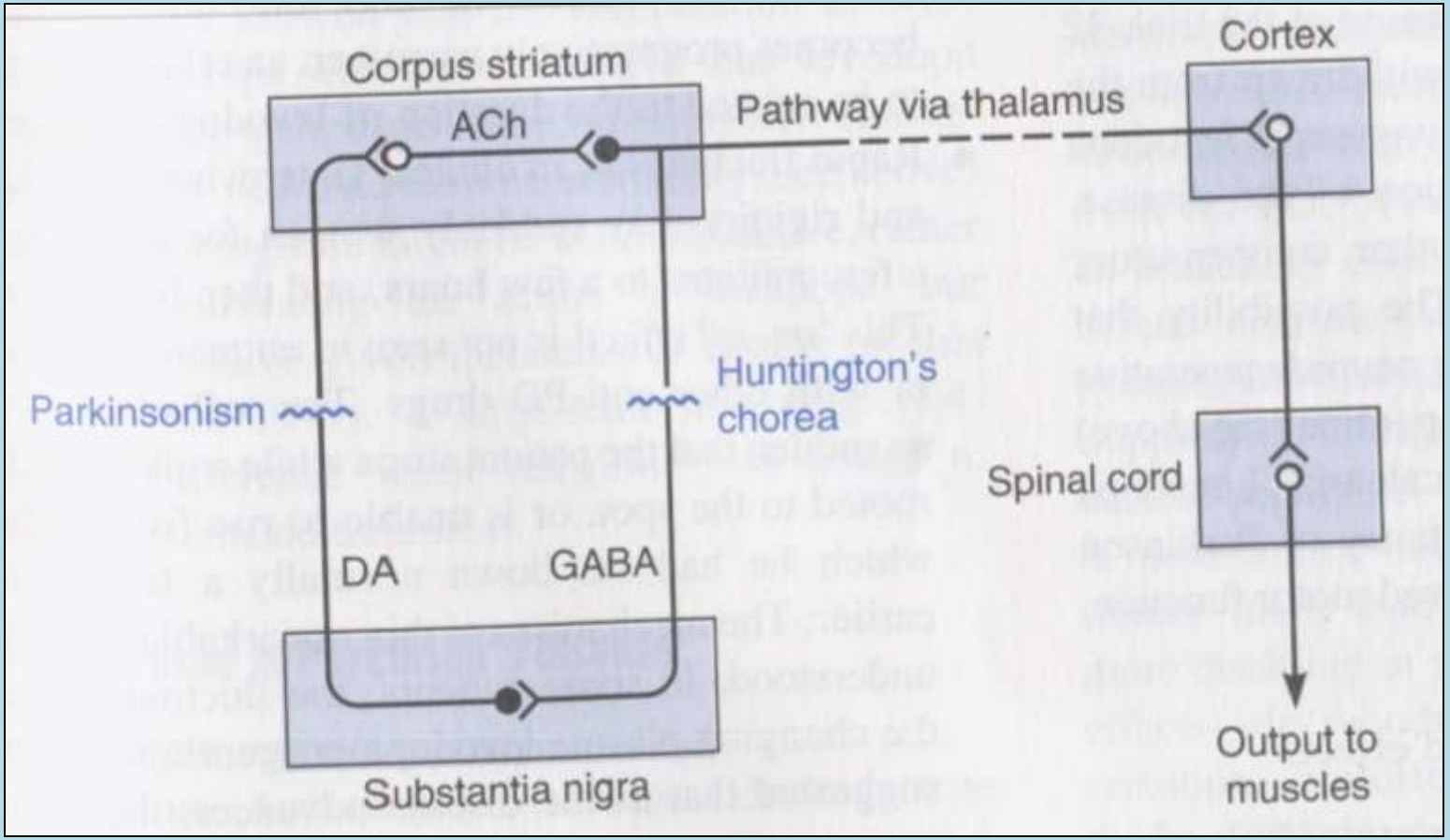
Ultimate cure may lie in stem cell therapy.



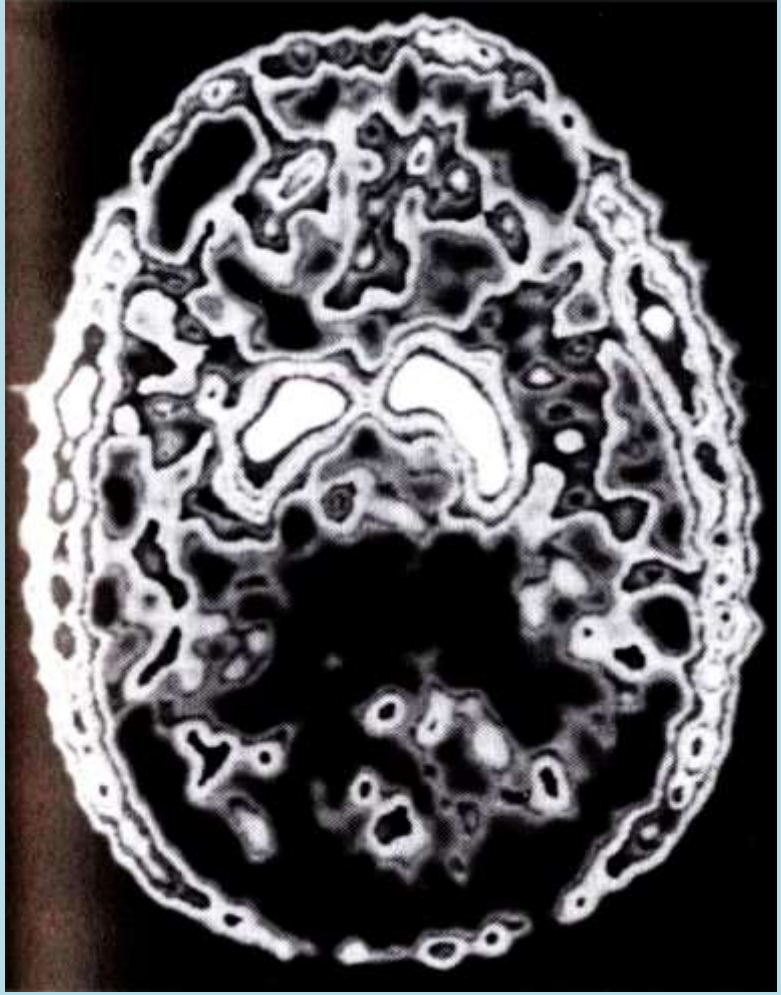
PARKINSONISM



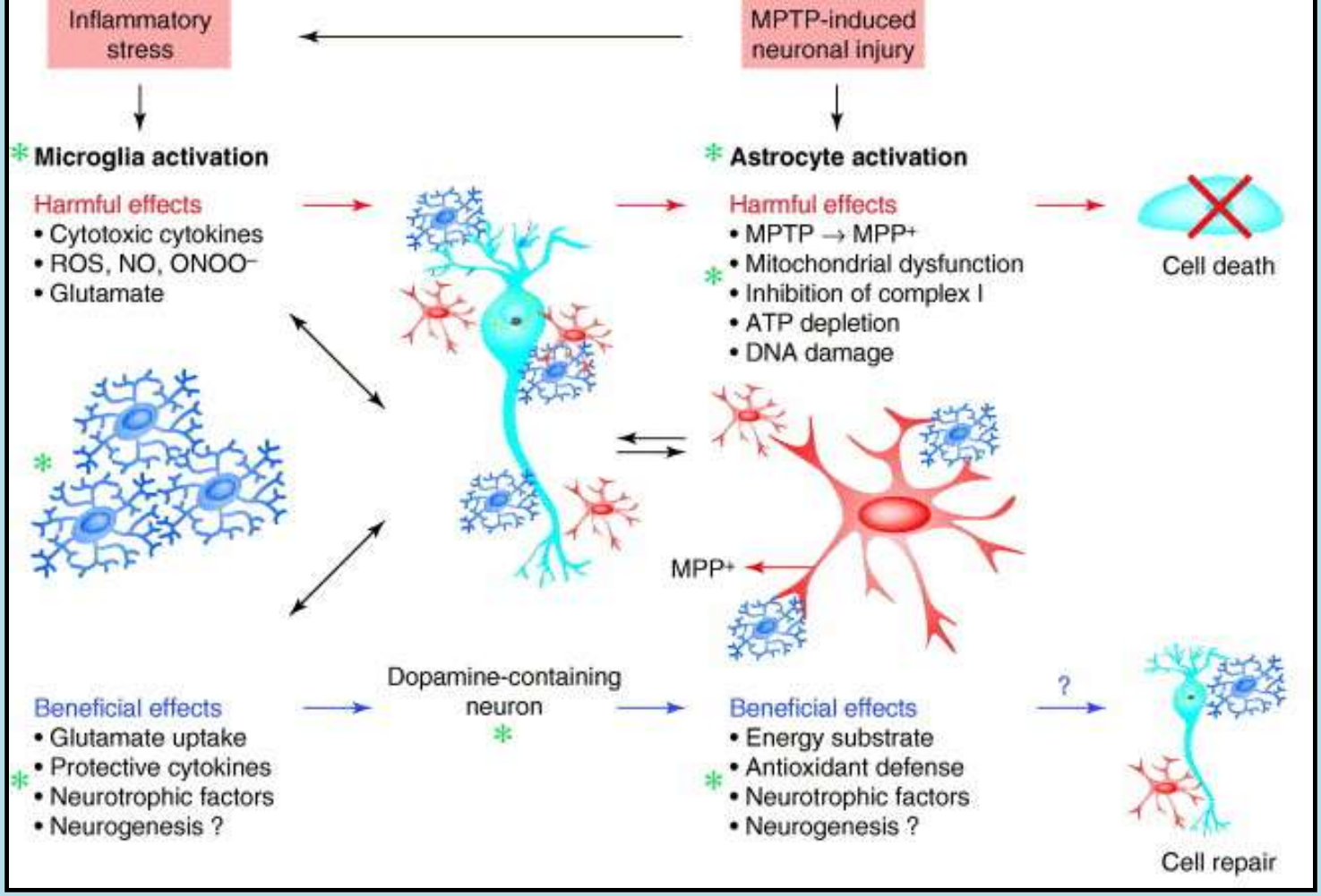
The impact of perinatal genetic, hormonal and environmental interactions on the inflammatory glial cell response and individual resistance or susceptibility to inflammatory diseases.



ACh release from the striatum is strongly inhibited by dopamine, and it is suggested that hyperactivity of these cholinergic neurons (associated with lack of dopamine) leads to symptoms of PD, whereas hypoactivity (associated with surfeit of dopamine, secondary to a deficiency of GABA) results in the hyperkinetic movements and hypotonia characteristic of Huntington's disease



Dopamine in the basal ganglia of human subject : The subject was injected with 5-fluro-dopa labeled with positron – emitting isotope 18F, which was localized 3 hours later by the technique of positron emission tomography. The isotope is accumulated (white areas) by the dopa-uptake system of the neurons of the basal ganglia, and to a smaller extent in the frontol cortex. It is also seen in the scalp and tempralis muscles



The detrimental and beneficial inflammatory pathways in Parkinson's disease (PD) and potential pharmacological targets. Dopamine-containing neurons in the substantia nigra (SN) represent a preferential target for inflammatory stressors as a result of: (i) enzymatic and non-enzymatic autooxidation of dopamine leading to the generation of hydrogen peroxide (H_2O_2); (ii) the high toxicity of dopamine metabolites; and (iii) the interactions between iron (which is highly concentrated in the SN) and H_2O_2 in the Fenton reaction, leading to the formation of highly toxic radicals

Parkinson's disease:

- Parkinson's disease (PD) is a degenerative disease of the basal ganglia causing causing tremor at rest, muscle rigidity and hypokinesia, often with dementia.
- PD is often idiopathic, but it may follow stroke, virus infection or can be drug-induced (antipsychotic drugs).
- PD is associated with early degeneration of dopaminergic nigrostriatal neurons, followed by more general neurodegeneration.
- PD can be induced by MPTP, a neurotoxin affecting dopamine neurons. Similar environmental neurotoxins, as well as genetic factors, may be involved in human PD.

Drugs used in Parkinson's disease:

- Drugs act by counteracting deficiency of dopamine in basal ganglia or by blocking muscarinic receptors. None of the available drugs affects the underlying neurodegeneration.

- The most effective drug is **levodopa**, a dopamine precursor that passes the blood-brain barrier; it is given with an inhibitor of peripheral dopa decarboxylase (e.g. **carbidopa**) to minimize side-effects. Sometimes a COMT (catechol O-methyltransferase) inhibitor (e.g. **entacapone**) is also given, to retard dopamine metabolism.

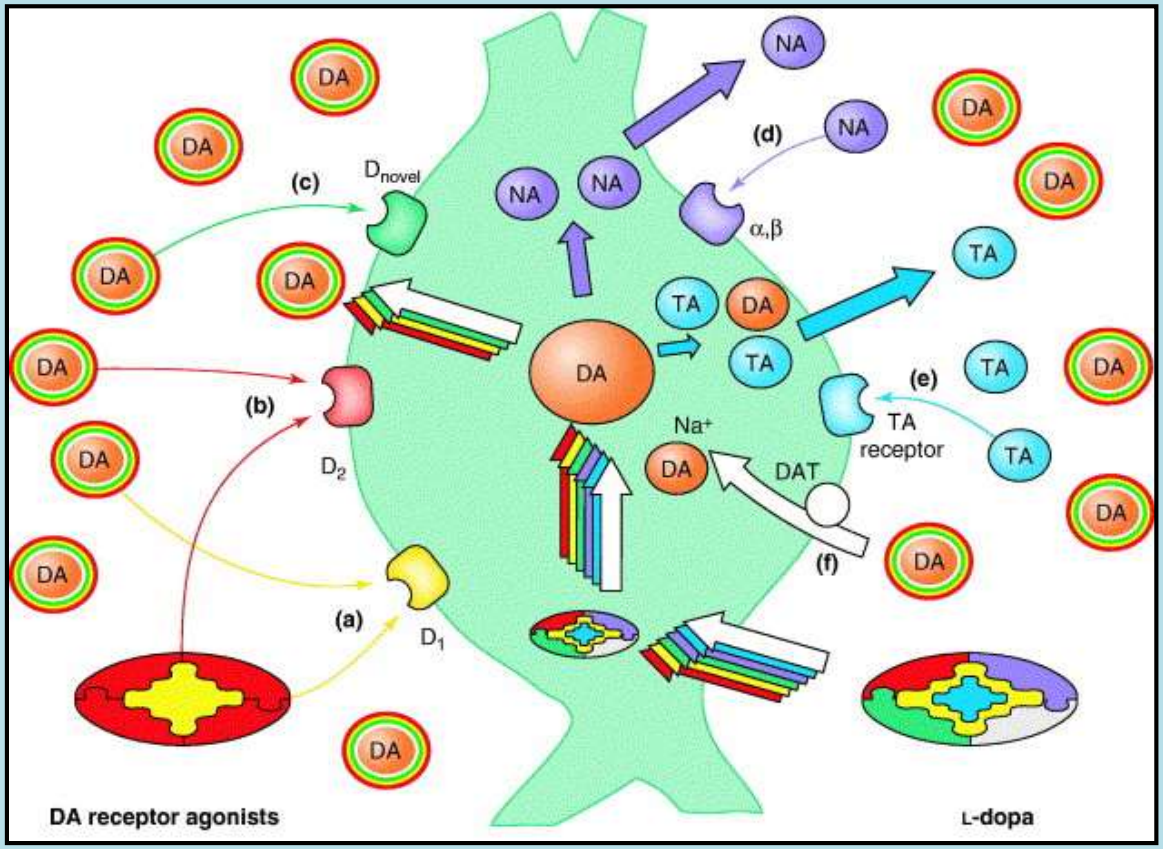
- Levodopa is effective in most patients initially but often loses efficacy after about 2 years.

Drugs used in Parkinson's disease:

- Main unwanted effects of levodopa are involuntary movements, which occur in most patients within 2 years, and unpredictable 'on-off effect'. Others are nausea, postural hypotension and occasionally psychotic symptoms.

- Other useful drugs include bromocriptine (dopamine agonist), selegiline (monoamine oxidase-B inhibitor), amantadine (?enhances dopamine release) and benztropine (muscarinic receptor antagonist, used for parkinsonism caused by antipsychotic drugs).

- Neurotrasplantation, still in an experimental phase, may be effective, but results are variable.



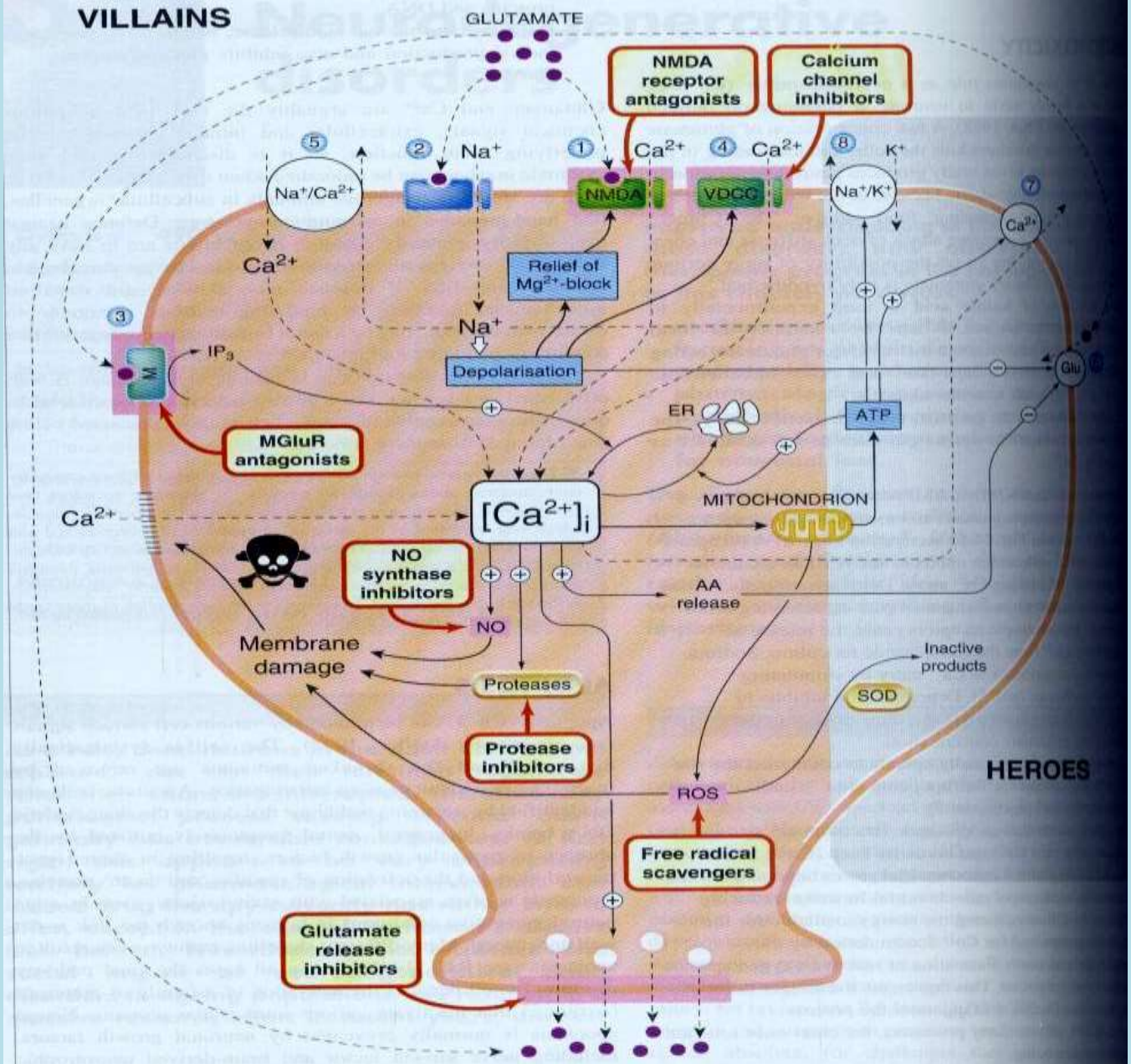
Several different pathways within central neurons are activated by l-dopa. Most of the neuronal responses to l-dopa are mediated by its metabolic transformation to dopamine (DA) and noradrenaline (NA). Similar to direct DA receptor agonists, DA, produced from l-dopa, activates D1-like receptors **(a)** and D2-like receptors **(b)** but, unlike direct DA receptor agonists, l-dopa also stimulates unconventional DA sites (D novel) **(c)**, and facilitates NA-mediated activation of α and β-adrenoceptors following its conversion to NA **(d)** and trace amine (TA)-mediated activation of TA receptors by regulating the release of TAs **(e)**. An additional effect of l-dopa therapy could result from an increased uptake of DA that co-transports depolarizing Na+ ions **(f)** into DA-containing neurons. These multiple effects of l-dopa that partially maintain synaptic wiring could account for the superior therapeutic response of l-dopa in PD when compared with direct D1-like and D2-like receptor agonists. Abbreviation: DAT, dopamine transporter.

ISCHAEMIC BRAIN DAMAGE

- After heart disease and cancer, strokes are the commonest cause of death and 70% that are non-fatal are the commonest cause of disability.

PATHOPHYSIOLOGY

- Interruption of blood supply to the brain initiates a cascade of neuronal events shown in figure; these lead in turn, to later consequences, including cerebral edema and inflammation, which can also contribute to brain damage.
- Further damage can occur following reperfusion, because of the production of ROS when the oxygenation is restored.
- Reperfusion injury may be an important component in stroke patients.
- These secondary processes often take hours to develop and may offer hope for therapeutic intervention.



Mechanisms of excitotoxicity. Membrane receptors, ion channels and transporters, identified by numbers 1–8, are discussed in the text. Possible sites of action of neuroprotective drugs (not yet of proven clinical value) are highlighted. Mechanisms on the left (villains) are those that favour cell death, while those on the right (heroes) are protective. See text for details. (ER, endoplasmic reticulum; AA, arachidonic acid; ROS, reactive oxygen species; SOD, superoxide dismutase; NMDA, *N*-methyl-D-aspartate; VDCC, coltage-controlled calcium channel; IP_3, inositol trisphosphate; NO, nitric oxide.)

Pathophysiology:

- The lesion produced by occlusion of a major cerebral artery consists of a central core in which the neurons quickly undergo irreversible necrosis, surrounded by a penumbra of compromised tissue in which inflammation and apoptotic cell death develop over a period of several hours.

- It is assumed that neuroprotective therapies, given within a few hours, might inhibit this secondary penumbral damage.

- Glutamate excitotoxicity plays a critical role in brain ischaemia.

Pathophysiology:

- Ischaemia causes depolarization of neurons, and the release of large amounts of glutamate.

- Calcium ion accumulation occurs, partly as a result of glutamate acting on NMDA receptors, for both Ca2+ entry and cell death following cerebral ischaemia are inhibited by drugs that block NMDA receptors or channels.

- NO also builds up, to levels much higher than can be produced by normal neuronal activity (i.e. to levels that are toxic, rather than modulatory).

THERAPEUTIC APROACHES

- In animal models involving cerebral artery occlusion, a long list of drugs targeted at the mechanisms shown in the figure can reduce the size of the infarct.

- These include glutamate antagonists, calcium and sodium channel inhibitors, free radical scavengers, anti-inflammatory drugs, protease inhibitors, and others. It seems that almost anything works.

- However, attempts to develop drugs for the therapeutic use have so far been disappointing.

THERAPEUTIC APROACHES

- The need to start therapy within hours of the attack is an additional problem. Many trials have been completed with few if any signs of efficacy.

- The dispiriting list of failures includes calcium and sodium channel blockers (e.g. nimodipine, fosphenytoin), NMDA receptor antagonists (selfotel, eliprodil, dextromethorphan), drugs that inhibit glutamate release (adenosine analogues, lobeluzole, drugs that enhance GABA effects (e.g. clormethiazole), and various free radical scavengers (.e.g. tirilazad).

HUNTINTGON'S DISEASE(HD)

- HD- Inherited (autosomal dominant) disorder.
- Trinucleotide repeat neurodegenerative disease, associated with the expansion of the number of repeats of CAG units of glutamine residues in the expressed protein.
- Protein coded by HD (huntingtin) interacts with various regulatory proteins including one of the caspases that participates in excitotoxicity and apoptosis- Neuronal loss, particularly in cortex and striatum resulting in dementia and severe involuntary jerky (choreiform) movements.
- Excess of dopamine & deficit of GABA.
- Treatment- Dopamine Antagonist (CPZ) & GABA agonist (Baclofen)

PRION DISEASES

- Spongiform encephalopathy (SE) in animals & humans
- BSE (Bovine Spongiform Encephalopathy)- transmissible to humans
- CJD (Creutzfeldt-Jakob Disease) unrelated to BSE, results from close contact with infected beef. Scrapie in sheep.
- Progressive and rapid dementia & loss of motor coordination.
- Responsible agent- Prion (protein)- cytosolic component. Altered glycosylation- Protein gets misfolded.
- Injection of “Prion” into mice causes SE but not in “Prion” knock out mice.
- Treatment- Clioquinol (Antimalarial) & CPZ. Inhibit aggregation.

Thank you