Alzheimer disease and neuroplasticity: New approaches and new targets in pharmacotherapy

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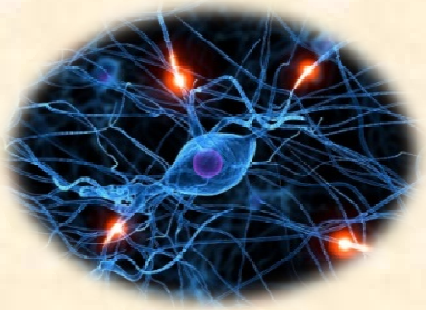
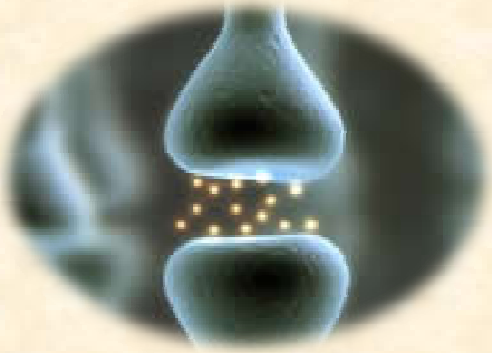
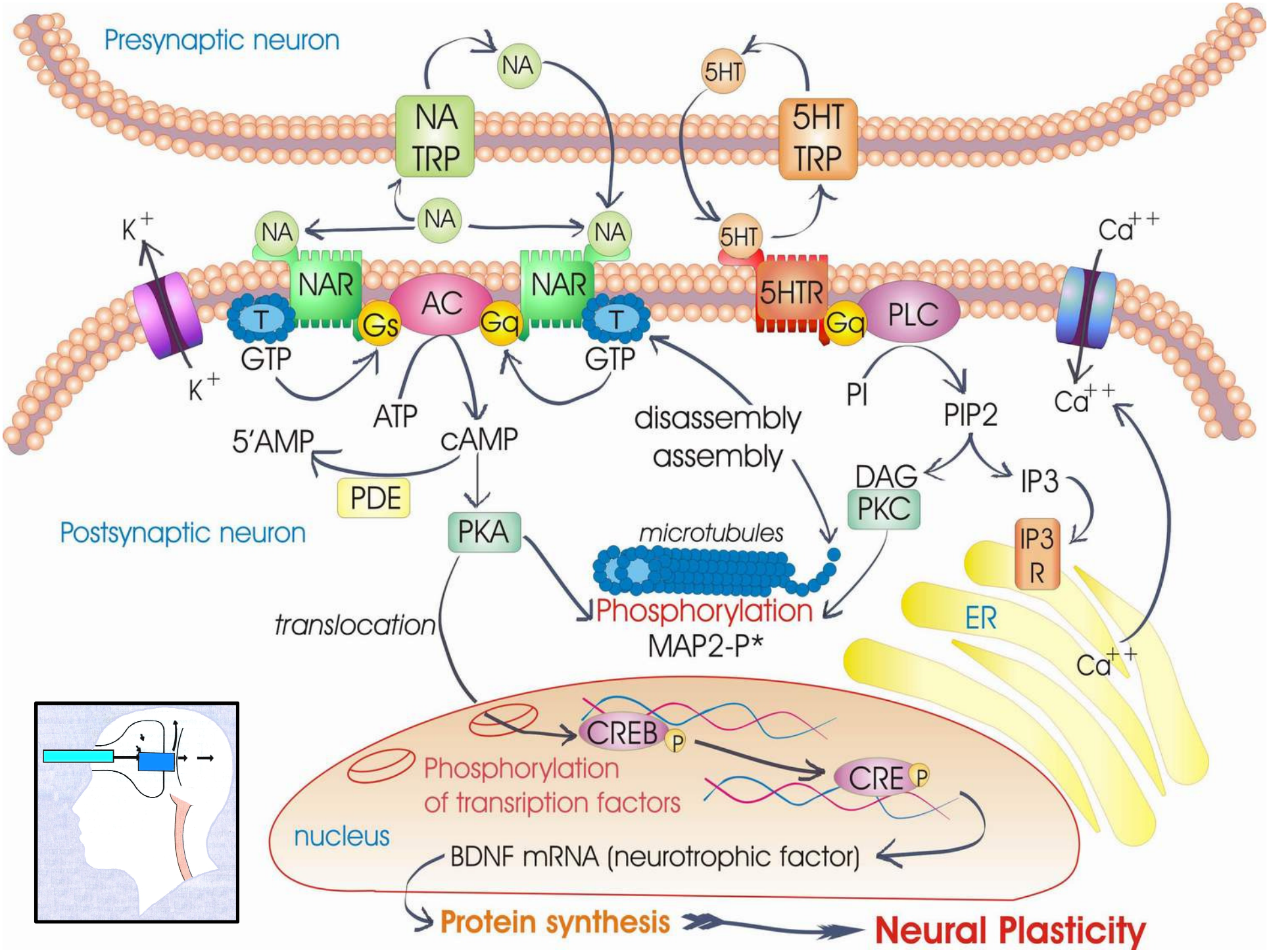
Neuroplasticity = Brain adaptation or synaptic adaptation)

- Neuroplasticity can briefly be defined as changes in the brain's neurons, and structural and functional changes in synapses formed by these neurons.
- It is due to reorganization and re-adaptation of some specific regions of brain.
- Sometimes the reorganization or readaptation mediate vital and important physiological events such as learning and memory by LTP.
- But sometimes especially under heavy stressful conditions, the reorganizations and readaptations are called as contra-adaptation and they are responsible for several pathological statements.





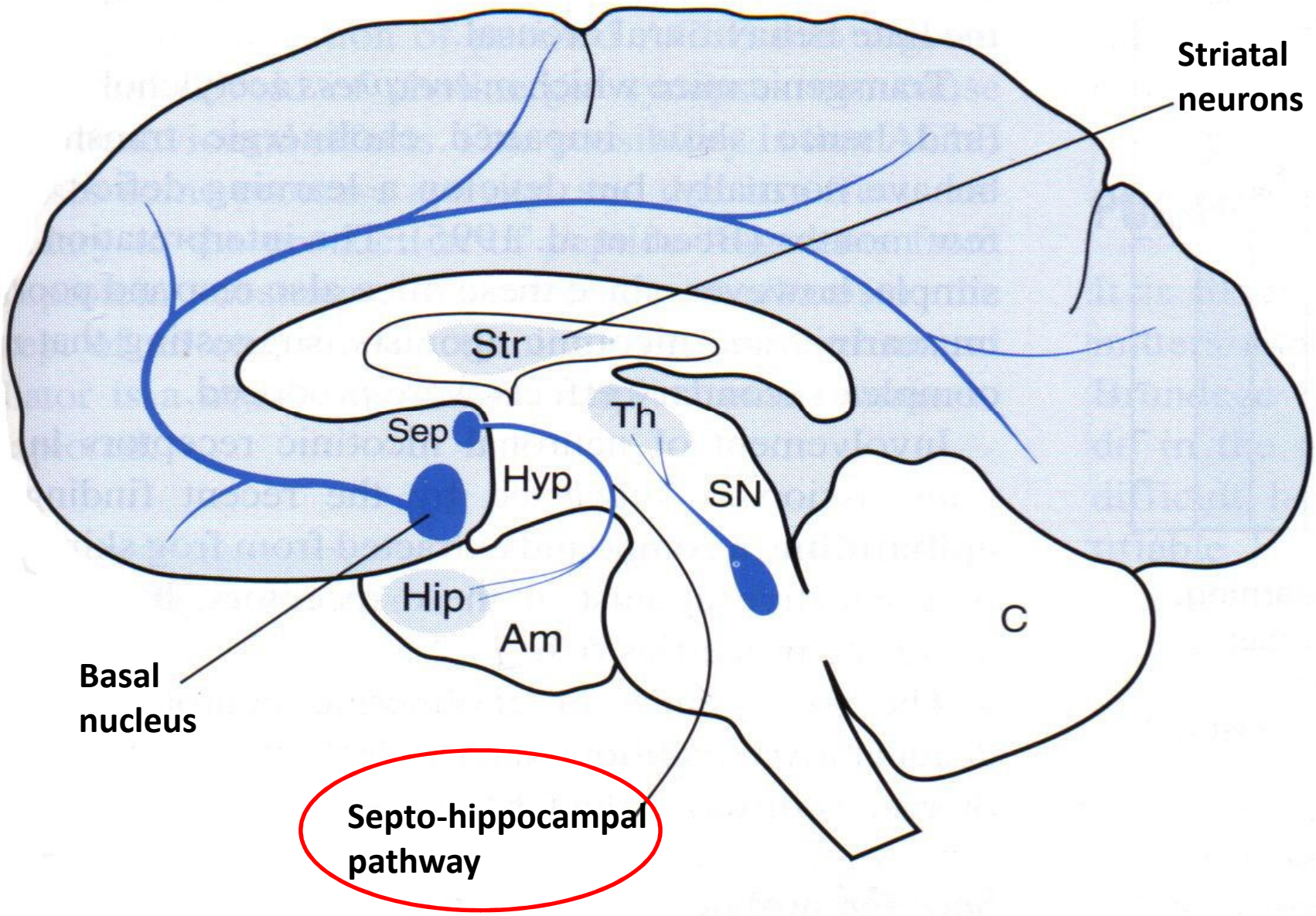
- Insufficient and/or perverted organizations in synapses or between the neurons causes the emergence of several diseases (Counter adaptation).
    - Alzheimer disease
    - Substance abuse and dependence
    - Schizophrenia
    - Depression
    - Autizm
- Thus, neuroplasticity can cause negative as well as positive changes
- Recovery of the pathological statements (recovery disorders) may also related to neuroplastic changes in brain.


Presynaptic neuron
NA
NA TRP
5HT
5HT TRP
K+
NA
NAR
T
GTP
Gs
AC
Gq
Ca++
5HTR
PLC
PI
PIP2
DAG
PKC
IP3
IP3 R
ER
ATP
cAMP
5'AMP
PDE
disassembly
assembly
Postsynaptic neuron
PKA
microtubules
Phosphorylation
MAP2-P*
translocation
CREB
P
CRE
Phosphorylation
of transription factors
nucleus
BDNF mRNA (neurotrophic factor)
Protein synthesis
Neural Plasticity

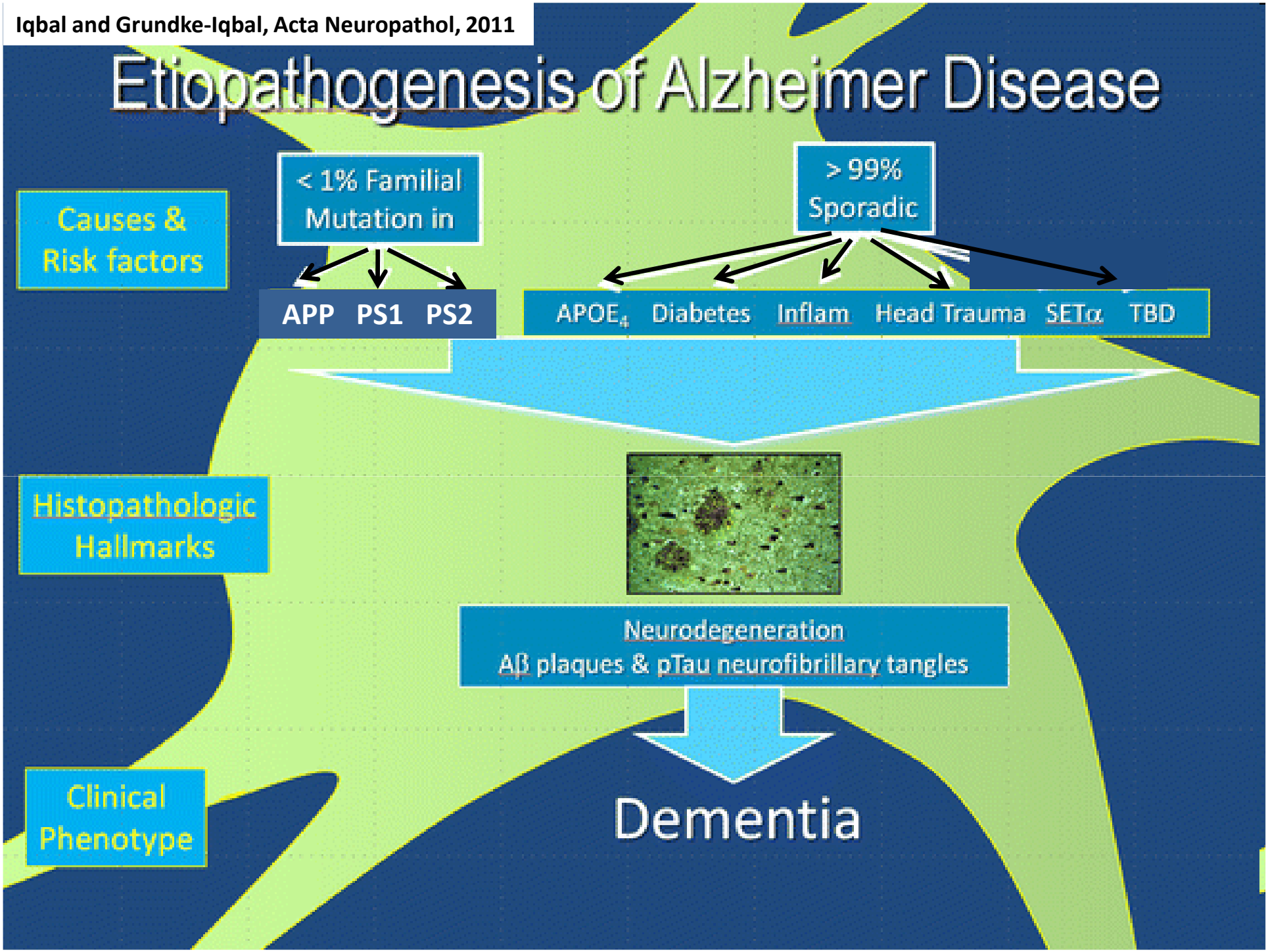
Neuroplasticity-induced changes in the brain

- Increase or decrease in dendritic branching
- New synapse formation or disappearance of present synapses
- Change in synaptic efficiency of present synapses
- Neurogenesis
- Apoptosis
- Changes in main brain metabolites
- Changes in survival of present neurons
- Increased resistance of neurons to breakage under stress
- Changes in stimulus-induced postsynaptic potentials of neurons
- Changes in activities of neurotrophic factors

The key pathway for Alzheimer disease

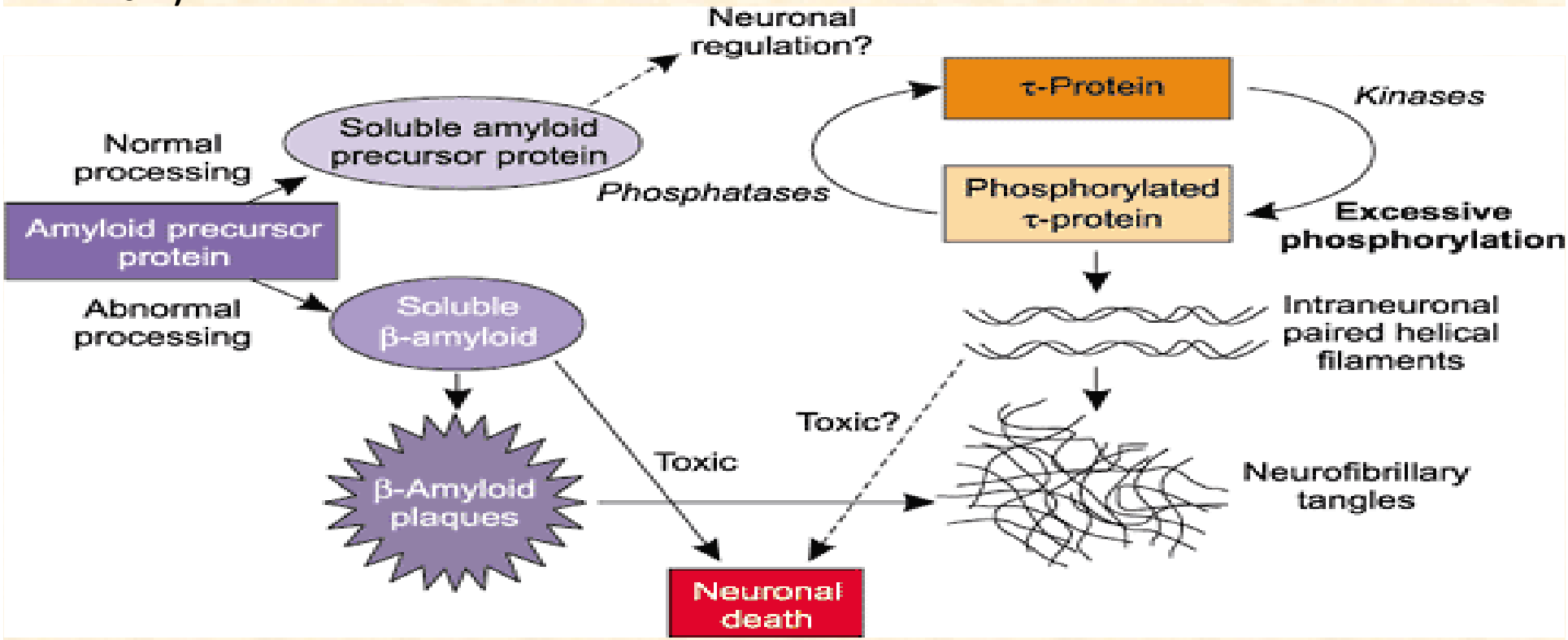


Iqbal and Grundke-Iqbal, Acta Neuropathol, 2011

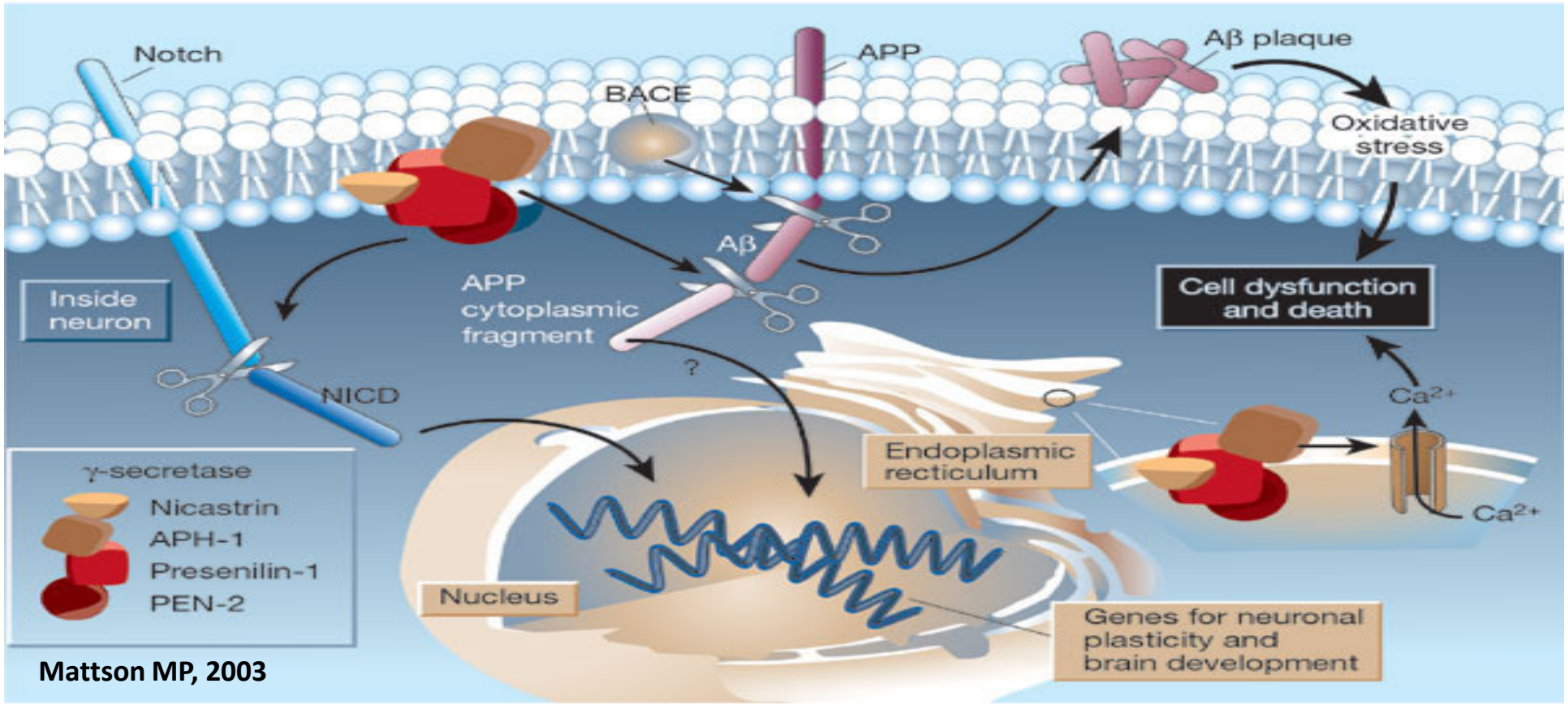


Formation of Aβ senil plaques

- Amyloid precursor protein (APP) is a membrane protein that has a role in the protection of synaptic integrity (Kang et al., 1987).
- Aβ is formed as a result of enzymatic breakdown of some peptide components from APP.
- They convert to highly insoluble and proteolysis-resistant fibrils called senile plaques by accumulation of toxic Aβ42 forms.
- Accumulation of $A\beta_{42}$ in brain inhibits LTP.
- Mutation of APP, PS1 and PS2 genes increases to produce Aβ42 formation (Galiberti and Scapini, 2012).

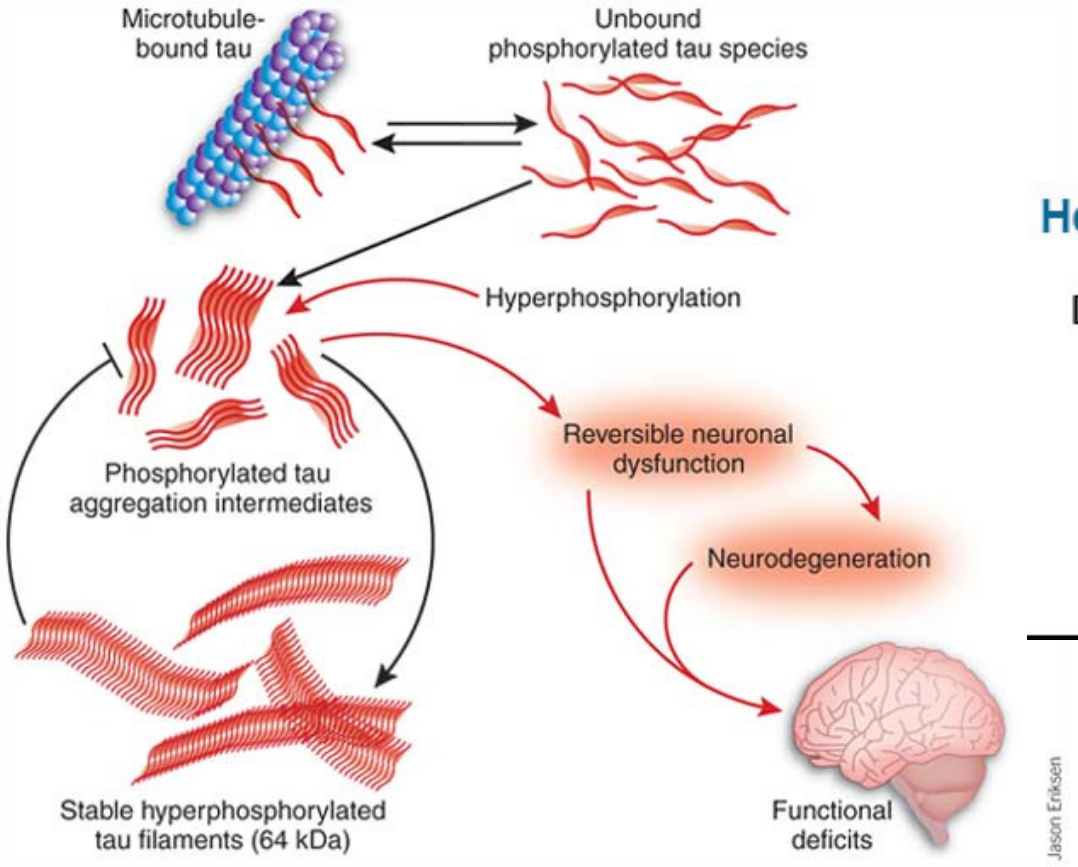


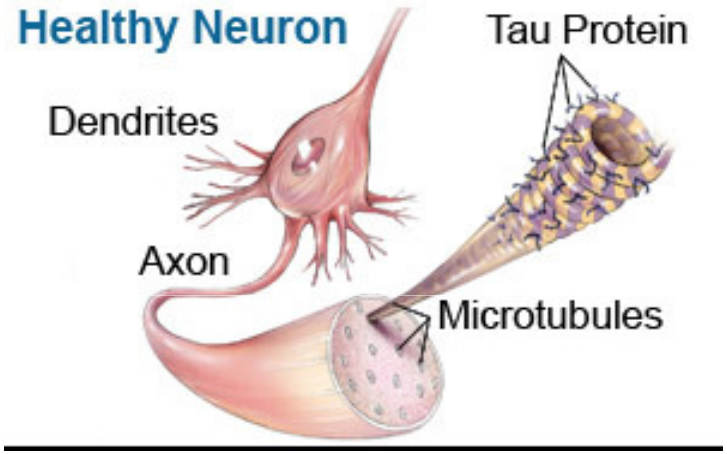
- **Notch is a cell surface receptor that, when activated by ligands such as Jagged and Delta, is cleaved at the membrane resulting in the release of «an intracellular domain of Notch» (NICD).**
- **NICD then translocate to the nucleus where it regulates the transcription of various genes.**
- **γ-secretase-mediated Notch signaling plays an essential role in the regulation of cell fate during development of many organ systems including the brain as indicated by embryonic lethality and defective neurogenesis that is identical in Notch and PS1-deficient mice (Shen et al., 1997)**
- **Mutations of PS1 and PS2 also disrupt constructive interaction and signaling in Notch pathway and increases diathesis to produce Aβ42 formation (Steiner et al., 2001).**



Mattson MP, 2003

Formation of neurofibrillary tangles (NFT)

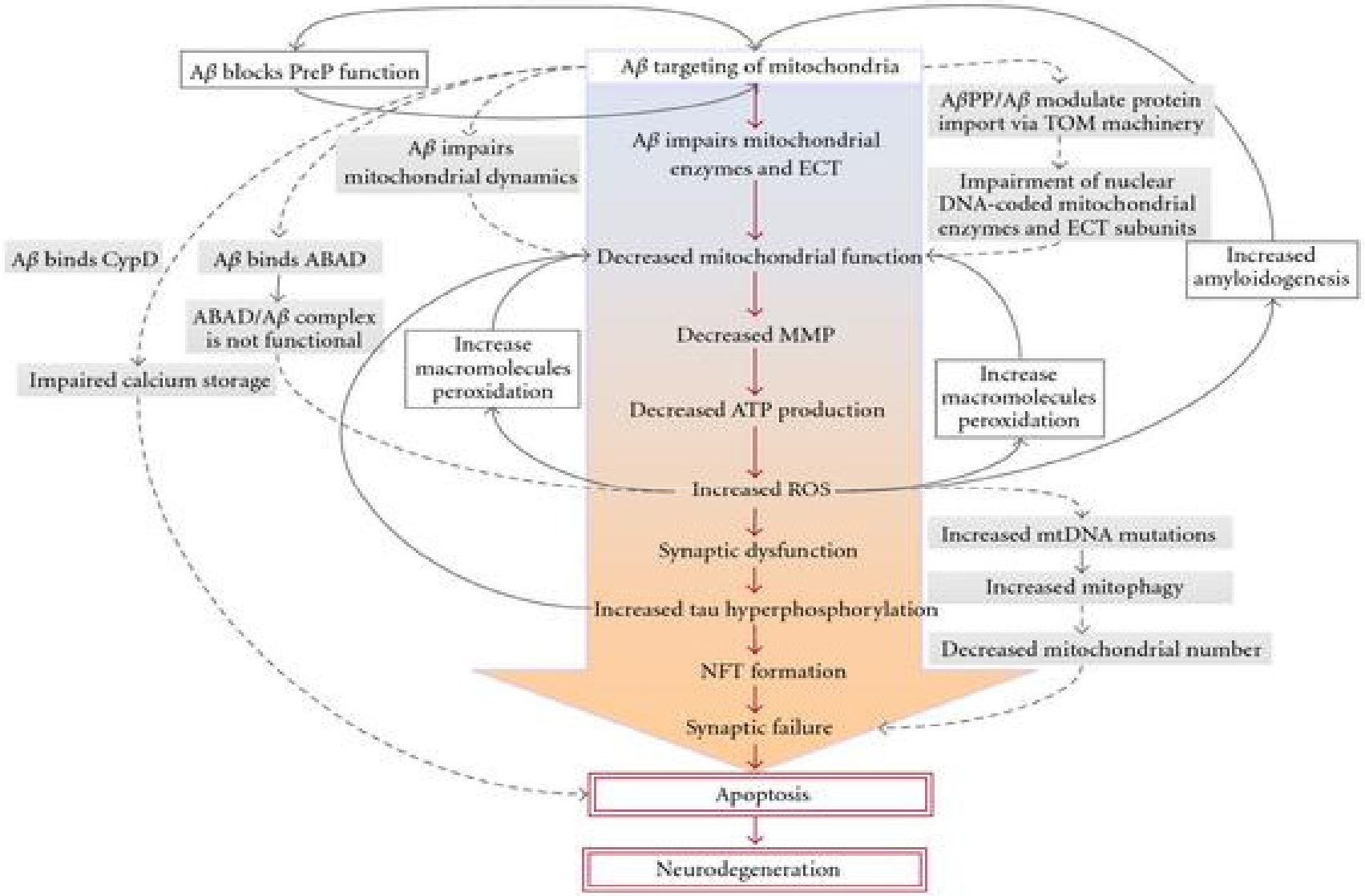




Microtubule-bound tau proteins release by hyprephosphorylation in presence of hyperactive kinases (GSK3β) and/or hypoactive phospahatases (PP2A).

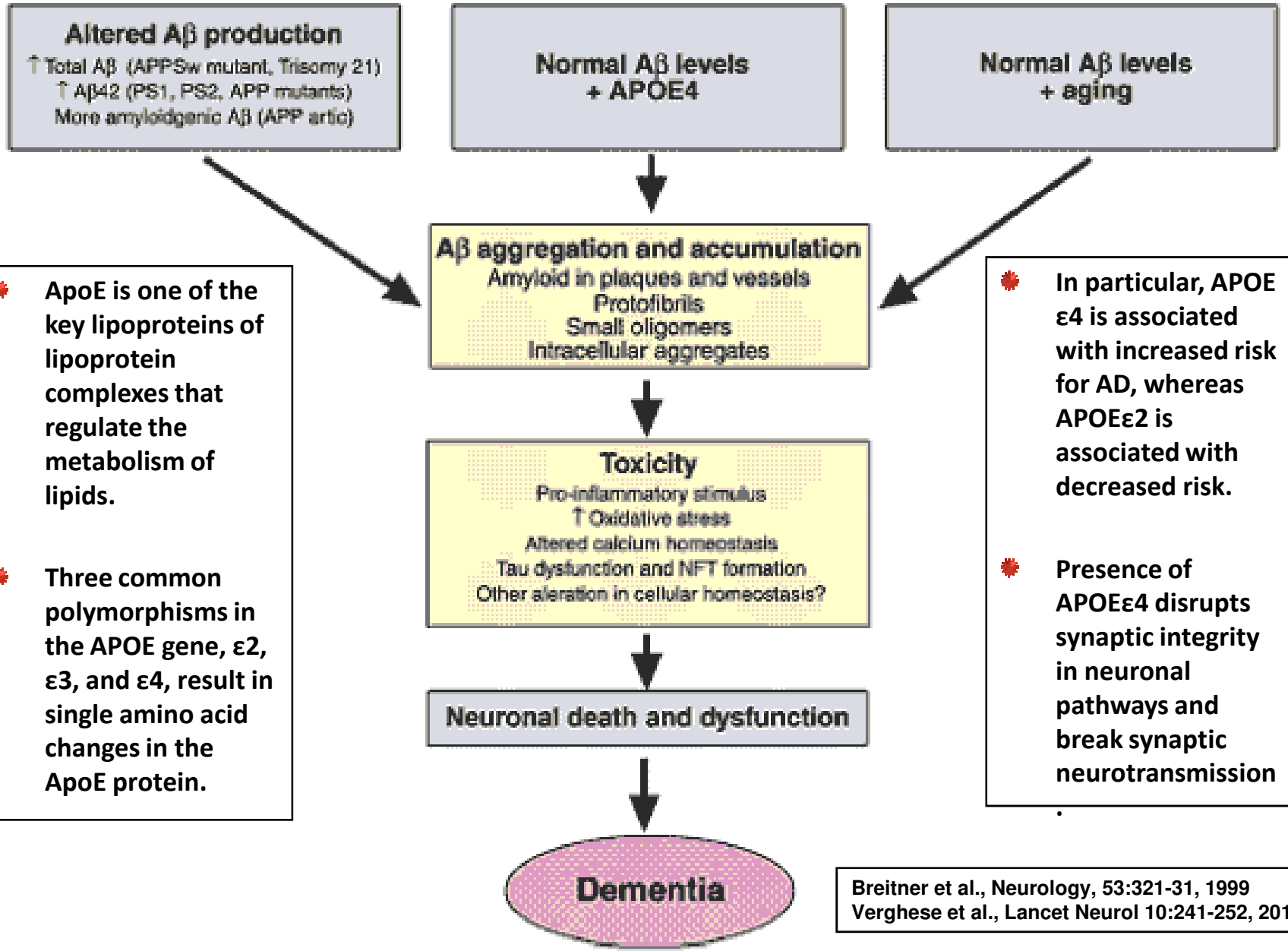
Free tau is converted double-stranded filaments (PHF) and these filaments produce NFTs.

http://www.innovitaresearch.org/



Accumulation of NFTs in synapses results in synaptic failure, apoptosis and neurodegeneration

http://www.innovitaresearch.org/



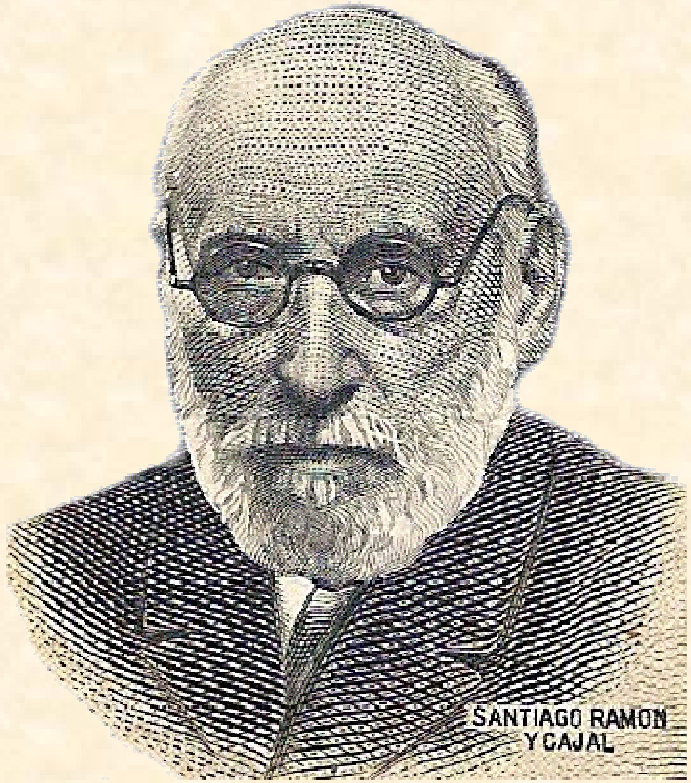
- ApoE is one of the key lipoproteins of lipoprotein complexes that regulate the metabolism of lipids.
- Three common polymorphisms in the APOE gene, ε2, ε3, and ε4, result in single amino acid changes in the ApoE protein.

- In particular, APOE ε4 is associated with increased risk for AD, whereas APOEε2 is associated with decreased risk.
- Presence of APOEε4 disrupts synaptic integrity in neuronal pathways and break synaptic neurotransmission

Breitner et al., Neurology, 53:321-31, 1999
Verghese et al., Lancet Neurol 10:241-252, 2011

Scientist who is the first defined neuroplasticity basis of Alzheimer disease

"One also might imagine that amnesia, a paucity of thought associations, retardation, and dementia could result when synapses between neurons are weakened as a result of a more or less pathological condition, that is, when processes atrophy and no longer form contacts, when cortical mnemonic or association areas suffer partial disorganization"
(Ramón y Cajal. Histologie du systeme nerveux. A. Maloine, Paris, 1911).



1852-1934, 1906 Nobel Prize

Neuroplasticity hypothesis of Alzheimer disease

- Indeed, AD is defined as a pathological remodelling characterized by memory failures, retardation of cognitive functions, and accompanying behavioral defects that appear due to an unreliable neurotransmission between hippocampus or other related limbic system formations, and entorhinal and associative cortex because of neuronal loses of these areas.

- The process is directly associated to senile plaques by accumulation of toxic Aβ42 and NFTs depending on excessive phosphorylation of tau.

Neuroplasticity changes in Alzheimer

- Dendritic and axonal alterations (especially in septo-hippocampal pathway)
  - Excessive growth of axon and dendrites in the regions forming senile plaques
- Neuronal losses (apoptosis) (especially in hippocampus, entorinal and associative regions cortex)
  - Activation of synaptic caspase
  - Damage in the ectopic cell cycle proteins such as proliferating cell (neuron) nuclear antigen (PCNA) making repair in DNA (it causes to produce Aβ)
- Synaptic losses in septohippocampal pathway
- Losses of other neurotransmitters (DA, NA, 5-HT)
  - Loss of motivation
  - Major depression
  - Psychotic symptoms
  - Distonia like Parkinson's disease

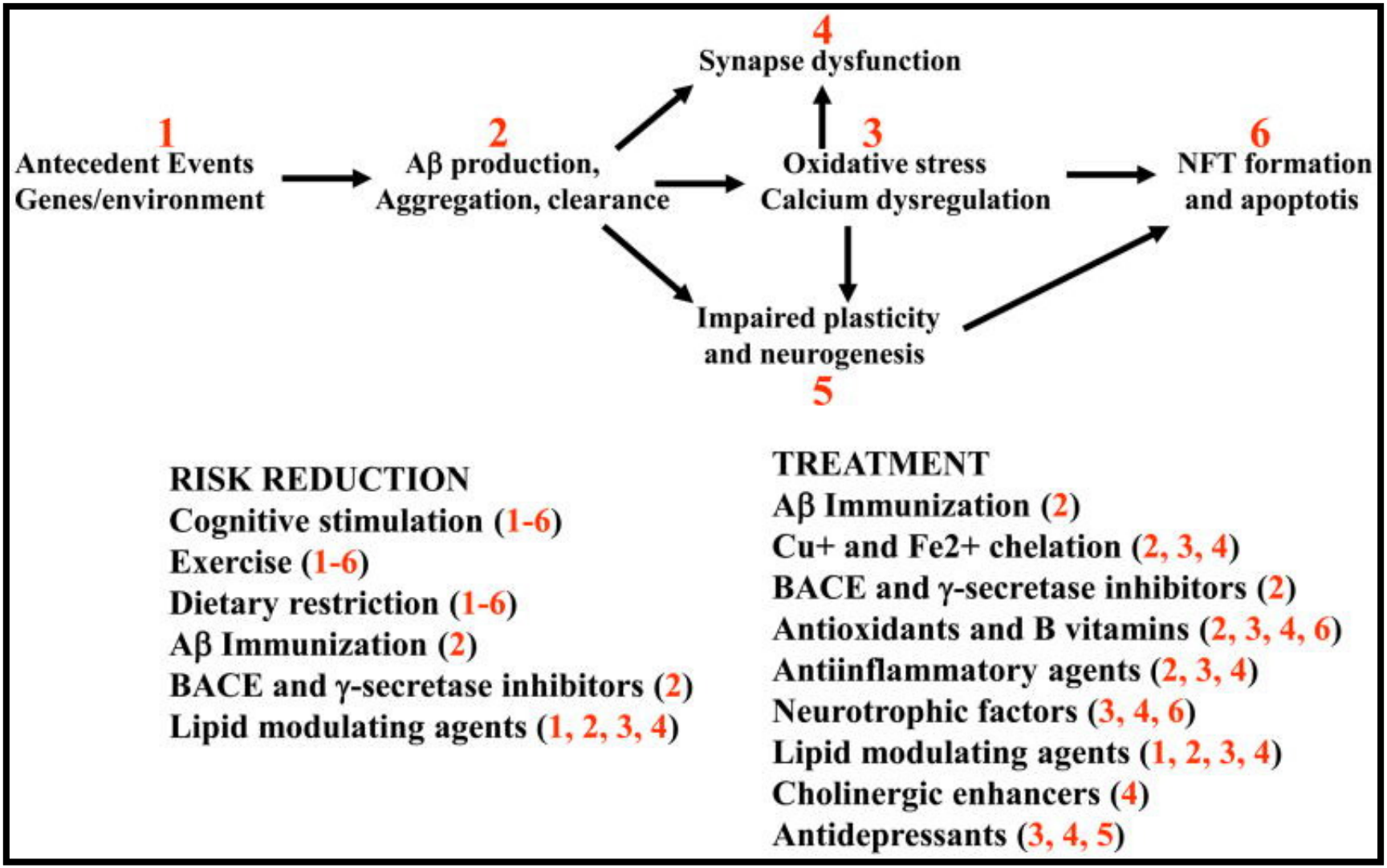
Neurotrophic factors in Alzheimer

- NGF has protective effect on cholinergic neurons.
  - In the absence of NGF, reduction in fiber density and down regulation of transmitter associates enzymes such as ChAT and AChE appear that results in a decrease of cholinergic transmission (Svendsen et al., 1991).
- BDNF also regulates synaptic plasticity and plays an important role in memory formation and storage.
  - Messenger RNA and protein levels of BDNF are found to be decreased in hippocampus and neocortex during AD (Murer et al., 2001).
  - Polymorphism of the BDNF has been implicated with higher risk for AD (Akatsu et al., 2006).
- Fibroblast growth factor-2 (FGF-2) is important in neuronal development and neuroprotection.
  - Increased levels and enhanced binding of FGF-2 were detected in senile plaques and neurofibrillary tangles in brain during AD (Kato et al., 1991; Stieber et al., 1996).

Current pharmacotherapy options

- AchE inhibitors (short elimination half-life, temporary and weak effect, narrow therapeutic index and some severe side effects)
  - Tacrine (hepatotoxicity and increases 3 times in serum ALT)
  - Donepezil (long effective selective inhibitor)
  - Galantamine (AchE inhibition + nicotinic receptor agonist in brain)
  - Rivastigmine (AchE and butrylcholine esterase inhibitor, dual effect)
- Memantine (Effective through glutamate system, NMDA antagonist)
- Others
  - Antioxidants (Ginko bloba, vitamin E, omega-3, melatonin, idebenon, green tea – polemical effects
  - Combinations with Vitamin B – polemical effects

- Like in other serious CNS diseases, AD treatment is also symptomatic and does not provide a rational solution.
- Present drugs are intended for delaying progression of the disease rather than to provide a capable treatment.



BACE: β *secretase*

Mattson MP, Nature, 2003

The drugs under investigation for treatment of Alzheimer disease

Action mechanisms	Agents	Statement
Anti-amyloid aggregation	Tramiprosate Colistrinin AZD103	Not continued Phase II Phase II
Vaccination	Bapineuzamab ACC-001 Solenezumab PF-04360365	Phase III Phase I Phase III Phase I
SALA (γ-secretase inhibition)	BMS-708163	Phase II
α-secretase potentiation	Etazolate	Phase II
Modulation of tau deposition	Methylene blue	Phase II
GSK inhibition	Lithium	İn progress
PPAR gamma agonist	Rosiglotazone	İn progress
Selective MAO-B inhibition	Selegiline	İn progress
5-HT4 agonist / AchE inhibitor	Donecopride	preclinical

SALA: Selective Aβ42-lowering agents; GSK: glycogen synthase kinase; PPAR: peroxisome proliferator activated receptor

Proc Natl Acad Sci U S A. 2014 Aug 25. pii: 201410315. [Epub ahead of print]

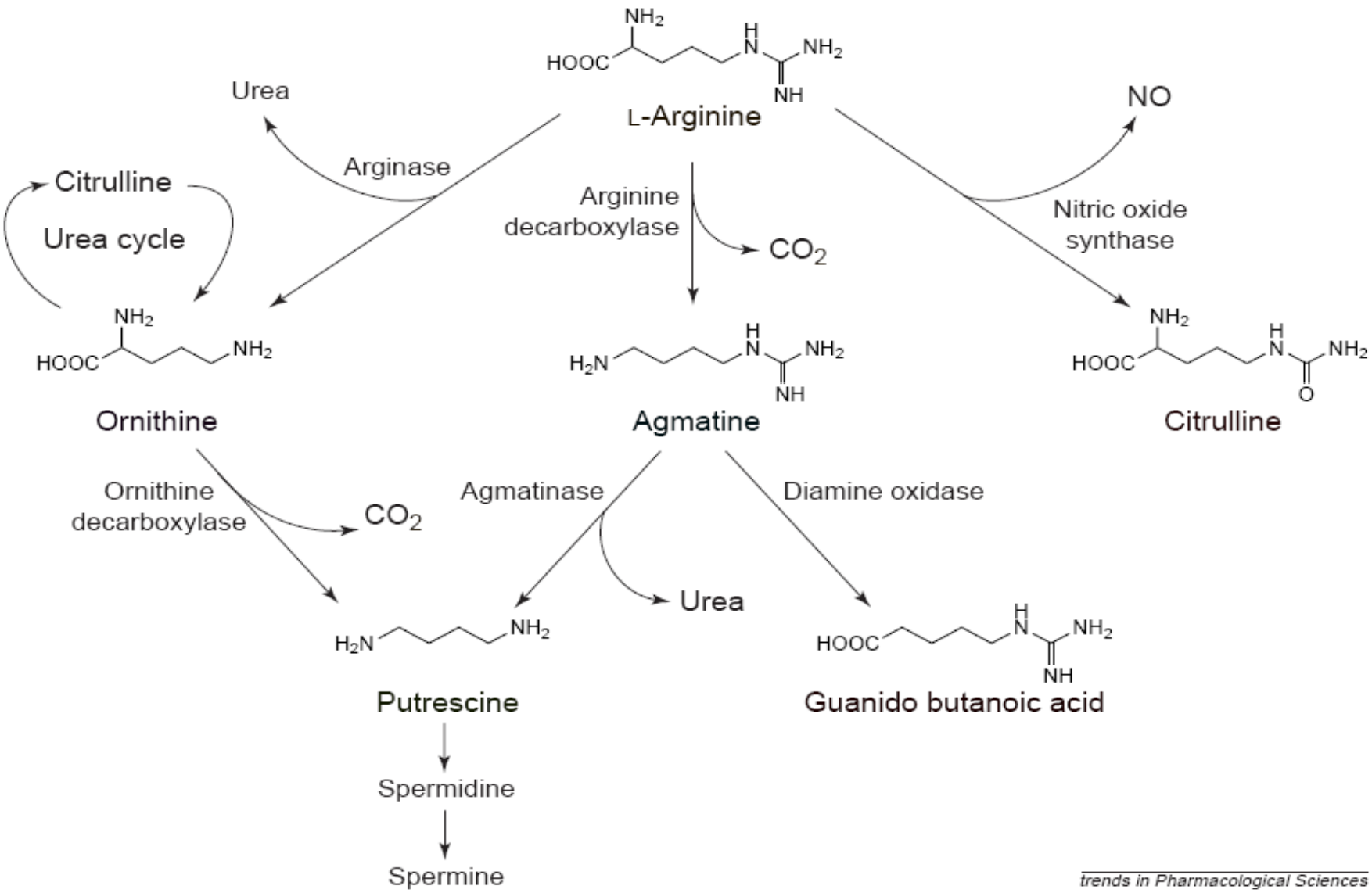
Design of donecopride, a dual serotonin subtype 4 receptor agonist/acetylcholinesterase inhibitor with potential interest for Alzheimer's disease treatment.

Lecoutey C[1], Hedou D[1], Freret T[2], Giannoni P[3], Gaven F[3], Since M[1], Bouet V[2], Ballandonne C[1], Corvaisier S[4], Malzert Fréon A[1], Mignani S[1], Cresteil T[5], Boulouard M[2], Claeysen S[3], Rochais C[6], Dallemagne P[6].

Université de Caen Basse-Normandie, Centre d'Etudes et de Recherche sur le Médicament de Normandie, F-14032 Caen, France

- The latter seems able to not only restore the cholinergic neurotransmission altered in AD but also, promote the secretion of a neurotrophic protein that is detrimental to the neurotoxic amyloid-β peptide.
- With its excellent drugability, donecopride further displayed significant procognitive effects in mice and generated a promising lead for a previously unidentified approach in AD treatment.
- Donecopride, as a druggable lead, was assessed for its in vivo procognitive effects (0.1, 0.3, 1 and 3 mg/kg) with an improvement of memory performances.

NO and polamines may be a new target for AD



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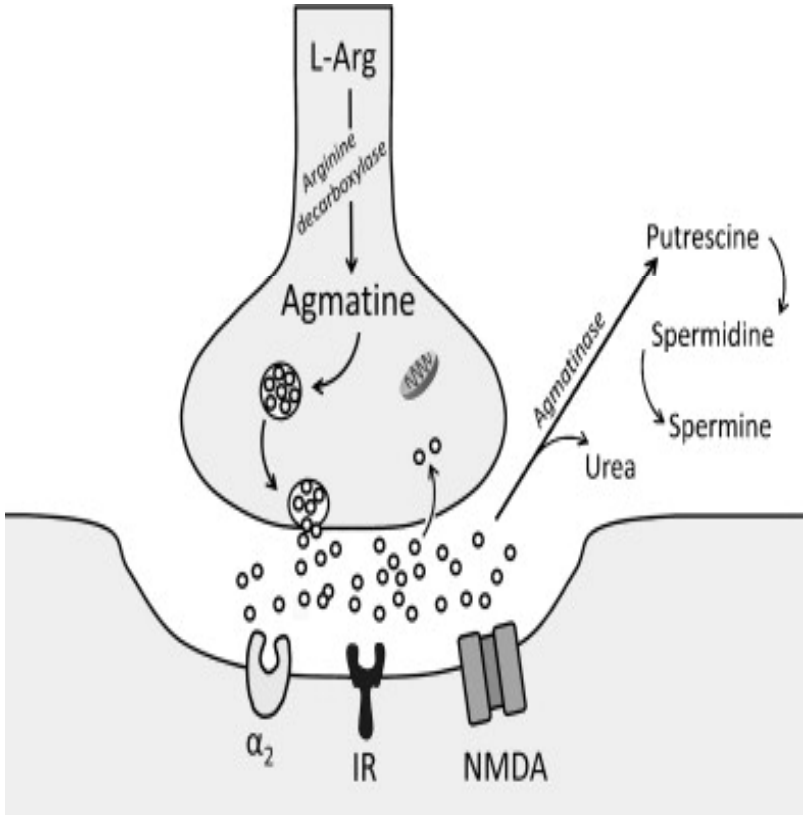
journal homepage: www.elsevier.com/locate/neubiorev

Review

The pharmacological importance of agmatine in the brain

Tayfun I. Uzbay*



- Agmatine is already accepted as a new neurotransmitter in CNS.
- Neuroprotective effects of agmatine were reported in animal studies (Kim et al., 2004; Kuo et al., 2007)

Neurobiol Aging. 2014 Sep;35(9):1992-2003. doi: 10.1016/j.neurobiolaging.2014.03.013. Epub 2014 Mar 20.

Altered arginine metabolism in Alzheimer's disease brains.

Liu P[1], Fleete MS[2], Jing Y[2], Collie ND[2], Curtis MA[3], Waldvogel HJ[3], Faull RL[3], Abraham WC[4], Zhang H[5].

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[4]Brain Health Research Centre, University of Otago, Dunedin, New Zealand; Department of Psychology, University of Otago, Dunedin, New Zealand.
[5]Brain Health Research Centre, University of Otago, Dunedin, New Zealand; School of Pharmacy, University of Otago, Dunedin, New Zealand.

Yonsei Med J. 2014 May;55(3):689-99. doi: 10.3349/ymj.2014.55.3.689. Epub 2014 Apr 1.

Agmatine improves cognitive dysfunction and prevents cell death in a streptozotocin-induced Alzheimer rat model.

Song J[1], Hur BE[2], Bokara KK[1], Yang W[1], Cho HJ[1], Park KA[1], Lee WT[1], Lee KM[3], Lee JE[2].

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[3]Department of Neurology, Seoul National University College of Medicine, Seoul, Korea.

Arginine metabolism is dramatically altered in diverse regions of AD brains, thus meriting further investigation to understand its role in the pathogenesis and/or progression of the disease, Liu et al., Neurobiol Aging, 2014

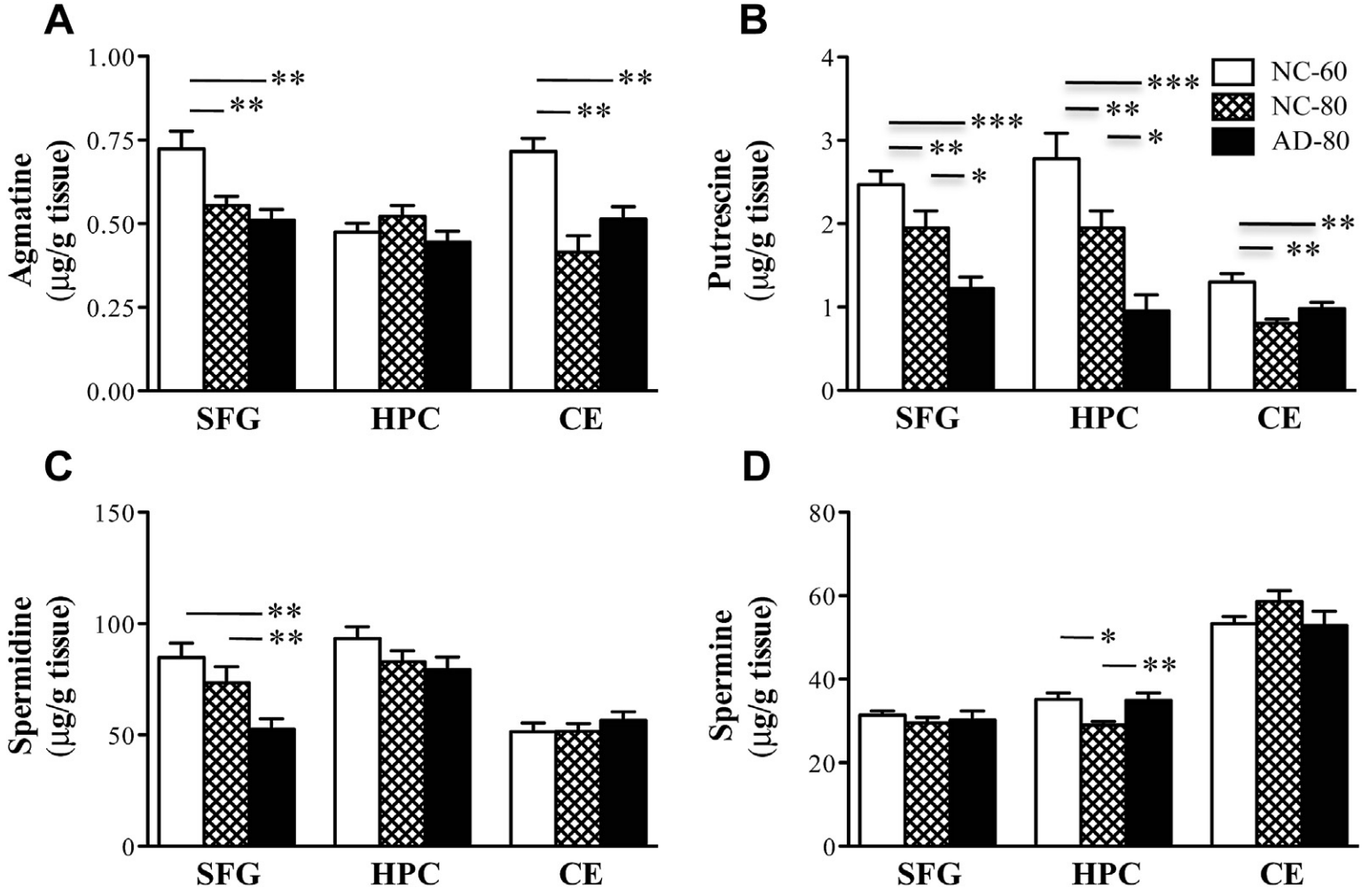


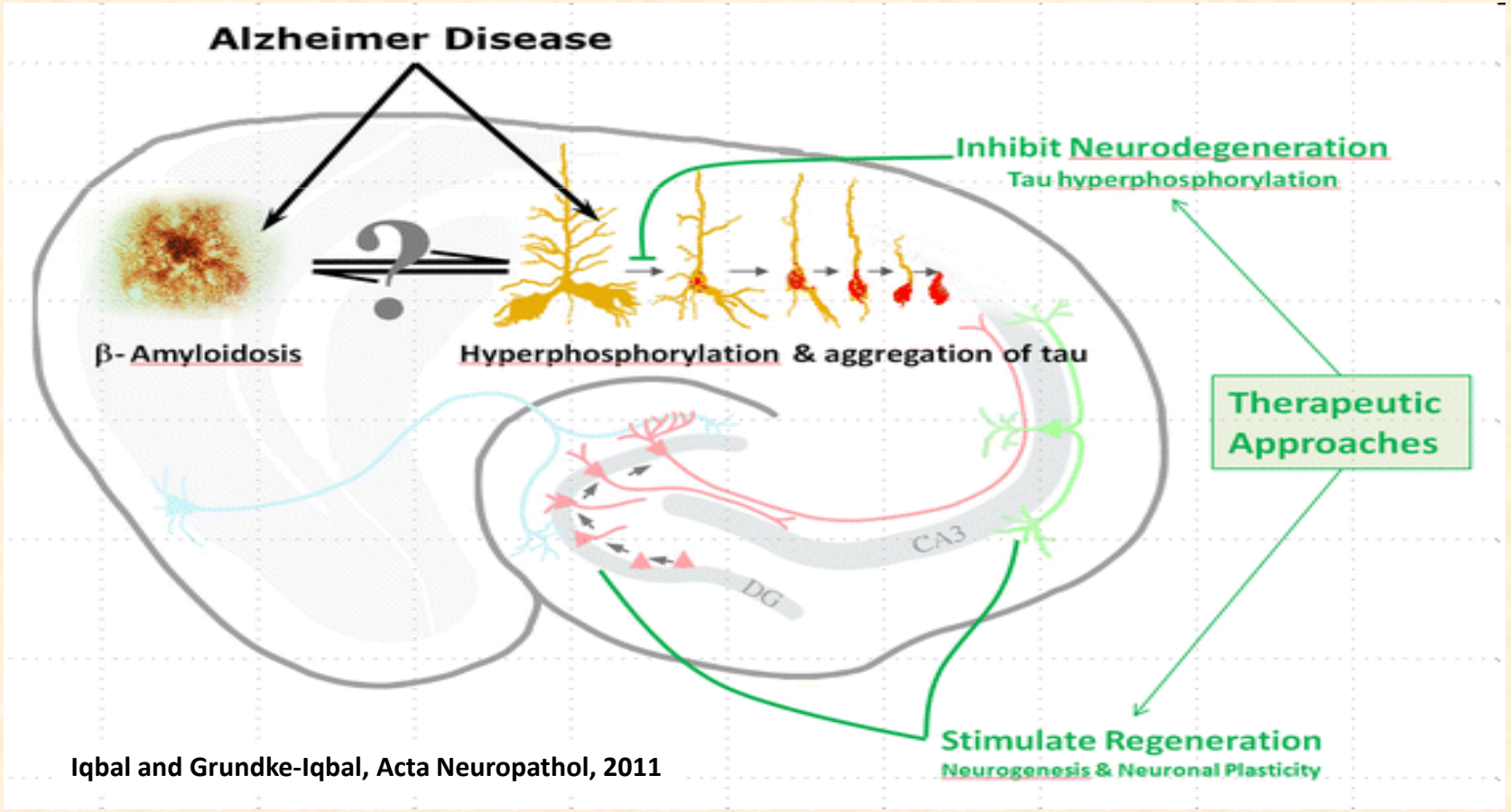
Fig. 6. (Mean ±SEM) agmatine (A), putrescine (B), spermidine (C) and spermine (D) levels in the superior frontal gyrus (SFG), hippocampus (HPC), and cerebellum (CE) from neurologically normal cases with an average age of 60 (NC-60) or 80 (NC-80) years, or Alzheimer's disease cases with an average age of 80 years (AD-80). Asterisks indicate significant differences between groups at * $p < 0.05$, ** $p < 0.01$, or *** $p < 0.001$. Abbreviation: SEM, standard error of the mean.

Some questions that we have to reply towards to radical solution in AD

- How can the better animal models be developed for Alzheimer studies?
- Could other neurotransmitter systems such as DA, NO, agmatin and other polyamines be new targets in development of new drugs and treatment of AD?
- Could etiopatogenezis of AD be related to neurodevelopmental processes like in autism and schizophrenia?
- How can we develop to our research strategies straight radical treatments?

Conclusions

- We have no drug that provide a radical treatment in AD.
- New trend in pharmacotherapy may be based on reversing the negative neuroplasticity.
- The agents that both inhibit neurodegeneration and stimulate regeneration may present more radical solutions via reversing the adverse neuroplasticity.



Iqbal and Grundke-Iqbal, Acta Neuropathol, 2011

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Thanks for your attention…