Le demenze: prospettive psicosociali, terapeutiche, assistenziali

Novità farmacologiche nel trattamento delle demenze

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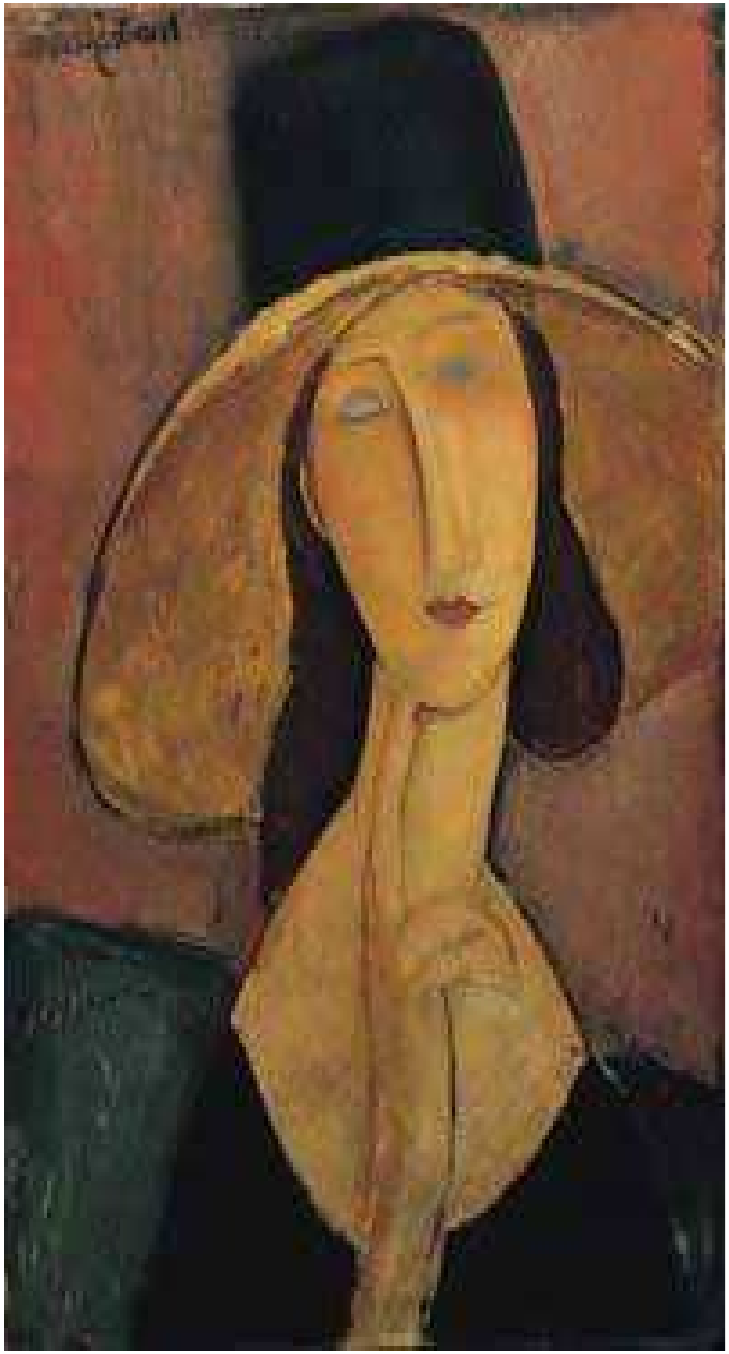
DEMENZA

- **Cronico e progressivo deterioramento delle funzioni**
- deficit della memoria (a breve e lungo termine)
- disturbi del linguaggio
- disturbi delle funzioni visuo-spaziali
- disturbi di altre funzioni cognitive (capacità di astrazione, di decisione, di calcolo etc.)
- alterazione della personalità



CLASSIFICAZIONE

Demenze degenerative (Alzheimer, Huntington, Parkinson etc.)

Demenze vascolari

Demenze a base infettiva

Demenze tossico-metaboliche

Pseudodemenza depressiva

Altri tipi

Alcuni dati……

Alzheimer è la più comune forma di demenza nel mondo

- Aumenta con età (1-2% a 65 anni, 35% o più a 85 anni)
- Nel 2000, in USA,almeno 4.5 milioni di malati
- Un nuovo caso di m. Alzheimer diagnosticato ogni 70 sec; ogni 33 sec nel 2050
- La stima è di 14 milioni di malati di Alzheimer nel 2010 (Mayeux, 2003), ovvero 1 malato ogni 85 persone nel mondo
- E' la settima causa di morte in USA; la quinta per fascia 65 anni e più (ed è in aumento)
- Ritardare di 1 anno l'età di comparsa e progressione dovrebbe portare a una riduzione di 9.2 milioni di casi nel 2050 (Brookmeyer et al, 2007).

… Alcuni dati…

- Almeno 10 milioni di persone in Europa e 25 milioni in tutto il mondo sono affette da m. Alzheimer
- Questa cifra è destinata a raddoppiare entro il 2030, quando, nel vecchio continente ci saranno circa 14 milioni di malati, e a crescere ancora
- La stima per il 2050 è di 115 milioni di persone che, nel mondo soffriranno di una qualche forma di demenza
- In Italia, più di 1 milione di affetti da demenza, almeno 600.000 con m. Alzheimer
- I costi sono elevatissimi (nel 2010, la Alzheimer Association ha stimato un costo di 172 miliardi di dollari)

FATTORI DI RISCHIO

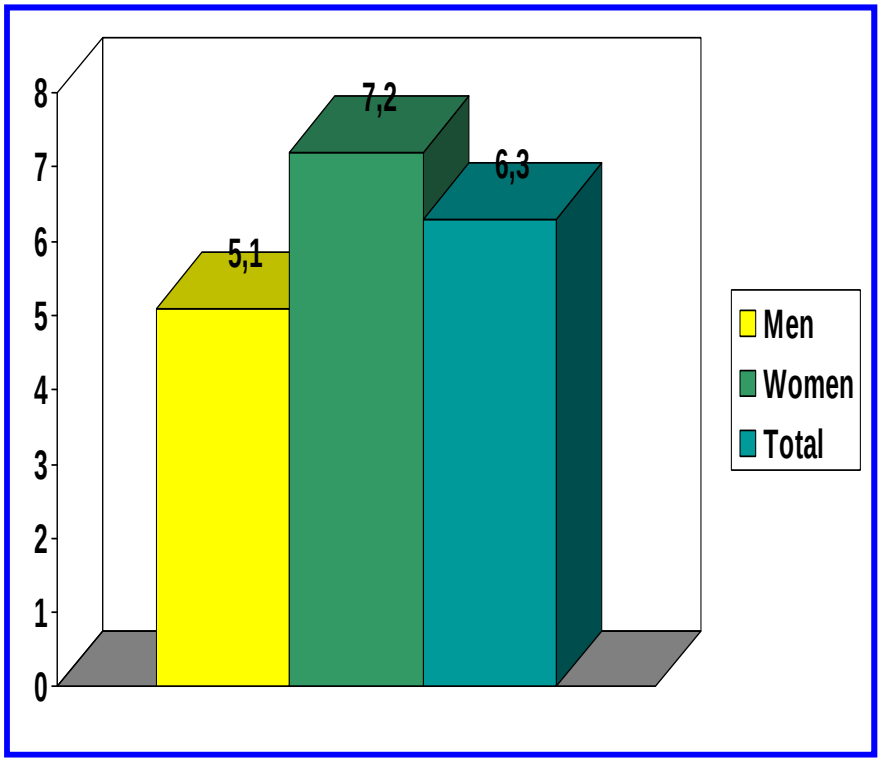
- **età**
- **storia familiare di demenza**
- **allele ε4 del gene ApoE**

(chi ha 1 ApoE ha rischio di AD >3; chi ha 2 geni ApoE e4 ha rischio > 12-15 volte)

- sesso femminile
- infezione virale
- ipolipemia

ApoE codifica per trasportatore di colesterolo

Prevalenza di demenza

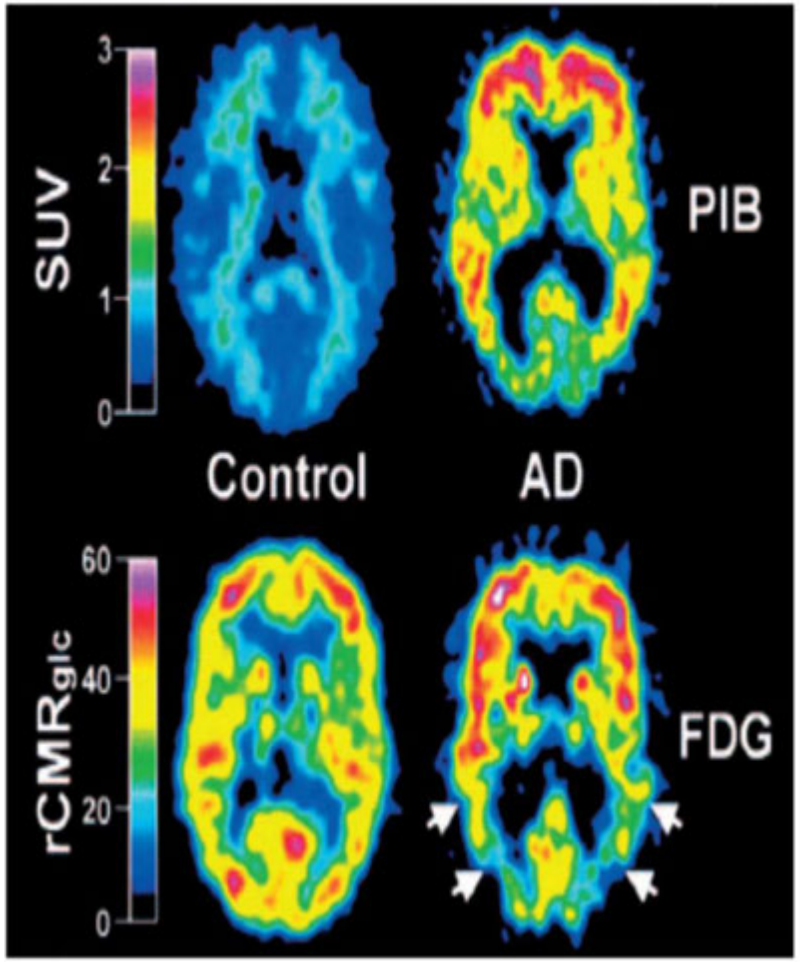


La prevalenza della demenza in Italia è più alta nelle donne che negli uomini (7,2% rispetto a 5,4% rispettivamente, nel gruppo di età 65-84 anni). Questa differenza è principalmente imputabile alla malattia di Alzheimer, più frequente nelle donne che negli uomini.

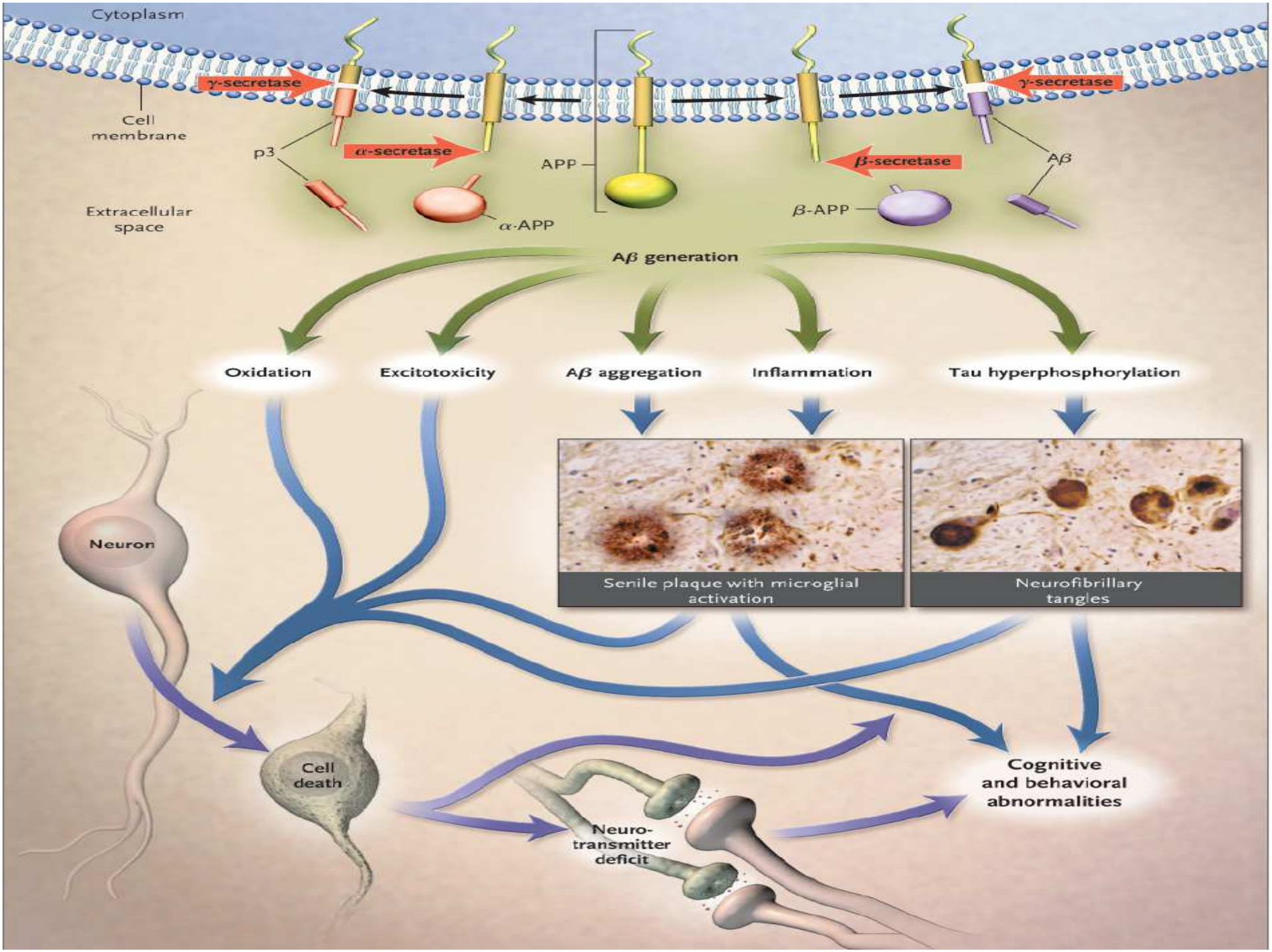
MORBO DI ALZHEIMER

- La diagnosi certa è basata sulla scoperta originale di Alzheimer: **il riscontro anatomo-patologico di placche senili** (depositi extracellulari di **beta-amiloide**), e **gomitoli neuro-fibrillari** (deposito intracellulare di filamenti, che contengono la **proteina tau** abnormemente fosforilata) **nel cervello dei pazienti**.

- Altra caratteristica importante è la **perdita sinaptica**: la **densità delle terminazioni presinaptiche è meno del 45 %**



Uomo 67 a, controllo (a sinistra)
Uomo 76 a, m. Alzheimer (a destra)


Cytoplasm
γ-secretase
Cell membrane
p3
α-secretase
APP
β-secretase
Aβ
Extracellular space
α-APP
β-APP
γ-secretase
Aβ generation
Oxidation
Excitotoxicity
Aβ aggregation
Inflammation
Tau hyperphosphorylation
Neuron
Senile plaque with microglial activation
Neurofibrillary tangles
Cell death
Neuro-transmitter deficit
Cognitive and behavioral abnormalities

DEMENZA TIPO ALZHEIMER

- placche senili
- degenerazione neurofibrillare
- perdita sinaptica

DEMENZA TIPO ALZHEIMER: alterazioni dei neurotrasmettitori

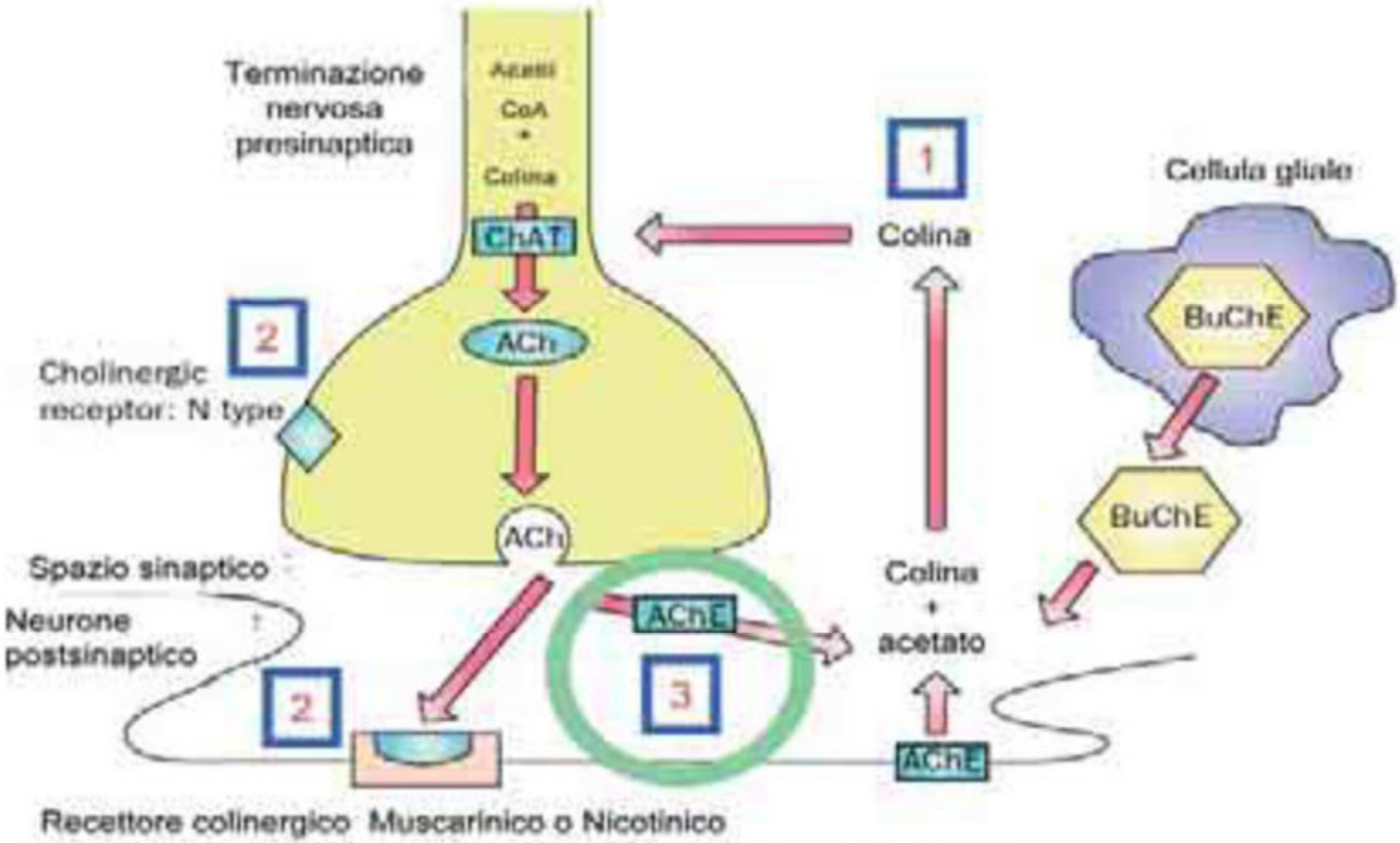
- **Sistema colinergico**
- **Sistema glutammatergico**
- sistemi noradrenergico, serotoninergico, dopaminergico

MORBO DI ALZHEIMER

- Nel m. Alzheimer è presente una **selettiva disfunzione del sistema colinergico** che ha un ruolo fondamentale nella regolazione dei circuiti della memoria a livello ippocampale, entorinale e del nucleo basale di Meynert.

- Nei pazienti affetti da Aizheimer si riscontra una notevole **diminuzione dei livelli di acetilcolina in queste aree cerebrali;** anche altri neurotrasmettitori risultano ridotti, ma è la **regolazione del tono colinergico il punto importante per tentare di rallentare la progressione della demenza**.

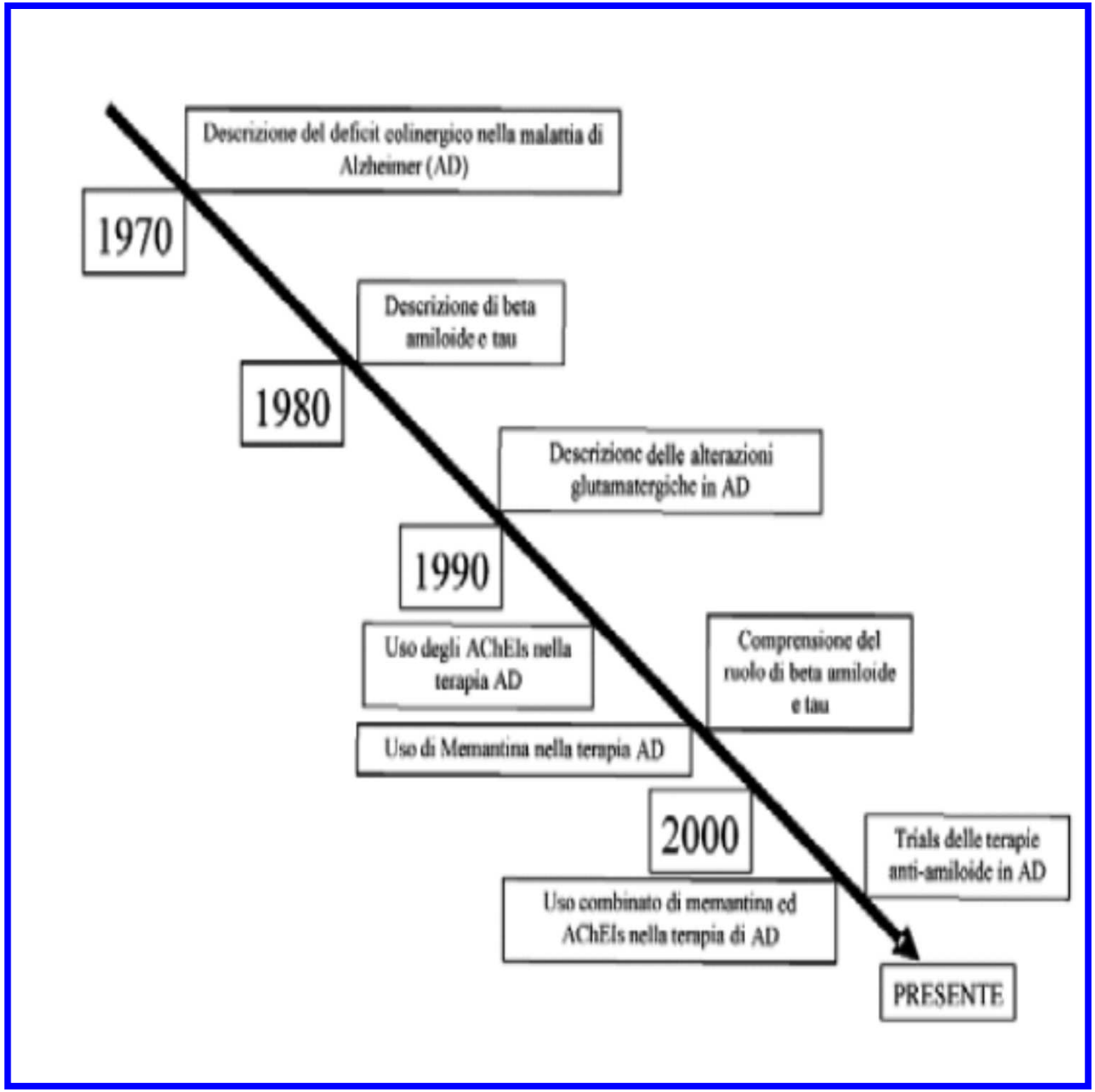
SINAPSI COLINERGICA



ACh: Acetilcolina; BuChE: Butirrilcolinesterasi; ChAT: colinoacetiltransferasi; CoA: coenzima A

Come potenziare i livelli di Ach

- somministrando colino-mimetici o pro-farmaci che generano Ach
- aumentando la liberazione di Ach
- "rinforzando" l'attività dei recettori nicotinici
- inibendo l'attività di acetil-colinesterasi (AChE),così da aumentare la concentrazione di Ach a livello sinaptico



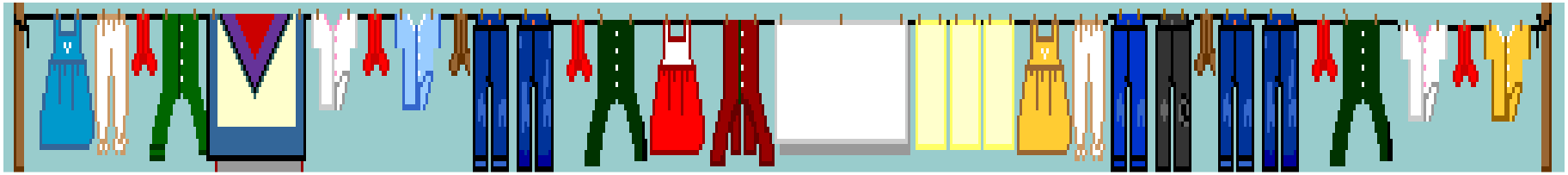
Racchi & Govoni, 2008

TERAPIA ATTUALE

- **Inibitori dell'enzima acetilcolinesterasi (AChE),** **allo scopo di aumentare il tono colinergico nei pazienti con demenza moderata o iniziale**

- **Questi farmaci non risolvono la demenza di Alzheimer**, ma, in una percentuale molto variabile di pazienti, migliorano le performances cognitive, il comportamento e generalmente la qualità di vita dei soggetti trattati.

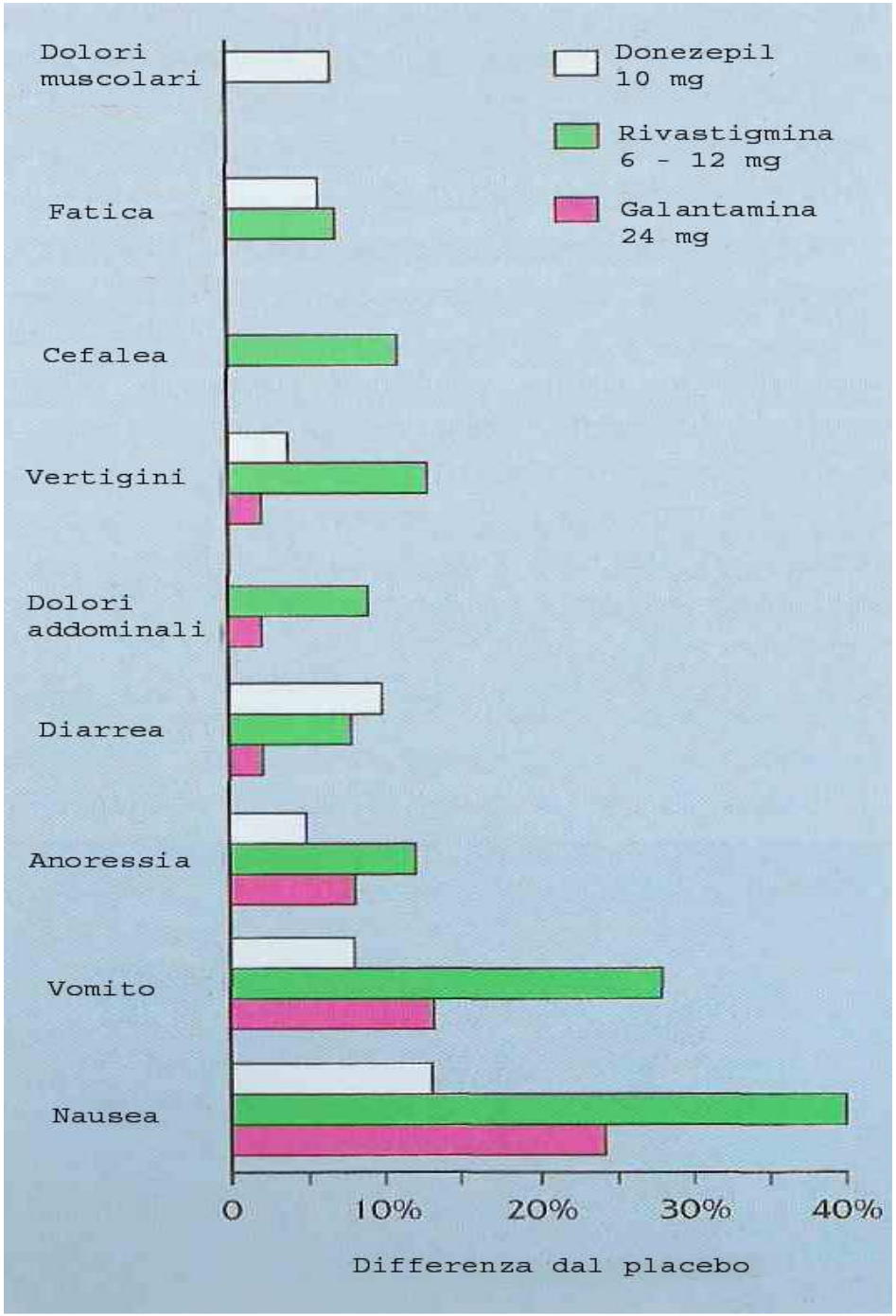
- I miglioramenti (quando ci sono) sono più evidenti nei pazienti con un grado di compromissione delle funzioni cognitive moderato, iniziale-intermedio ed anche nel cosiddetto "mild cognitive impairment (MCI)", ovvero la fase di transizione tra il normale rallentamento delle facoltà cognitive nell'anziano ed i primi segni di degenerazione e di demenza precoce.



Tab. I. Il trattamento farmacologico della malattia di Alzheimer.

Classe	Molecola	Meccanismo	Dose iniz. (mg/die)	Dose max* (mg/die)	N. somm./die
Inibitori acetilcolinesterasi	Donepezil	Inibizione dell'acetilcoline-sterasi, aumento delle concentrazioni sinaptiche di acetilcolina	5	10	1
	Galantamina		8	24	2
	Rivastigmina		3	12	2-3
Antagonisti recettore glutammato tipo NMDA	Memantina	Antagonismo reversibile dei recettori NMDA del glutammato	5	20	2

* La dose massima deve essere raggiunta gradualmente nel tempo



EFFETTI COLLATERALI DEGLI INIBITORI DELLE COLINESTERASI

- Glutammato è neuro-trasmettitore eccitatorio
- Ampiamente distribuito nel SNC
- Responsabile di Long Term Potentiation
- Responsabile di eccitotossicità con morte neuronale, a concentrazioni extracellulari elevate (50 – 100 mM).
- La presenza di beta Amiloide potenzia la eccito-tossicità

MEMANTINA

- **Antagonista non competitivo con bassa o moderata affinità per i recettori NMDA del glutammato.**
- Biodisponibilità del 100%, picco plasmatico a 3-7 ore, basso legame alle proteine plasmatiche; poco metabolizzata, t 1/2 circa 60-80 ore, metaboliti poco attivi sui recettori NMDA.
- Usare con attenzione nei pazienti con moderata ipofunzionalità renale (< dosaggio), sconsigliata nei pazienti con funzionalità renale compromessa.
- Le reazioni avverse più frequenti sono: agitazione, confusione, emicrania, costipazione.
- La memantina (associabile al donepezil) può migliorare *le performances* cognitive ed il comportamento anche in Alzheimer moderato-severo.

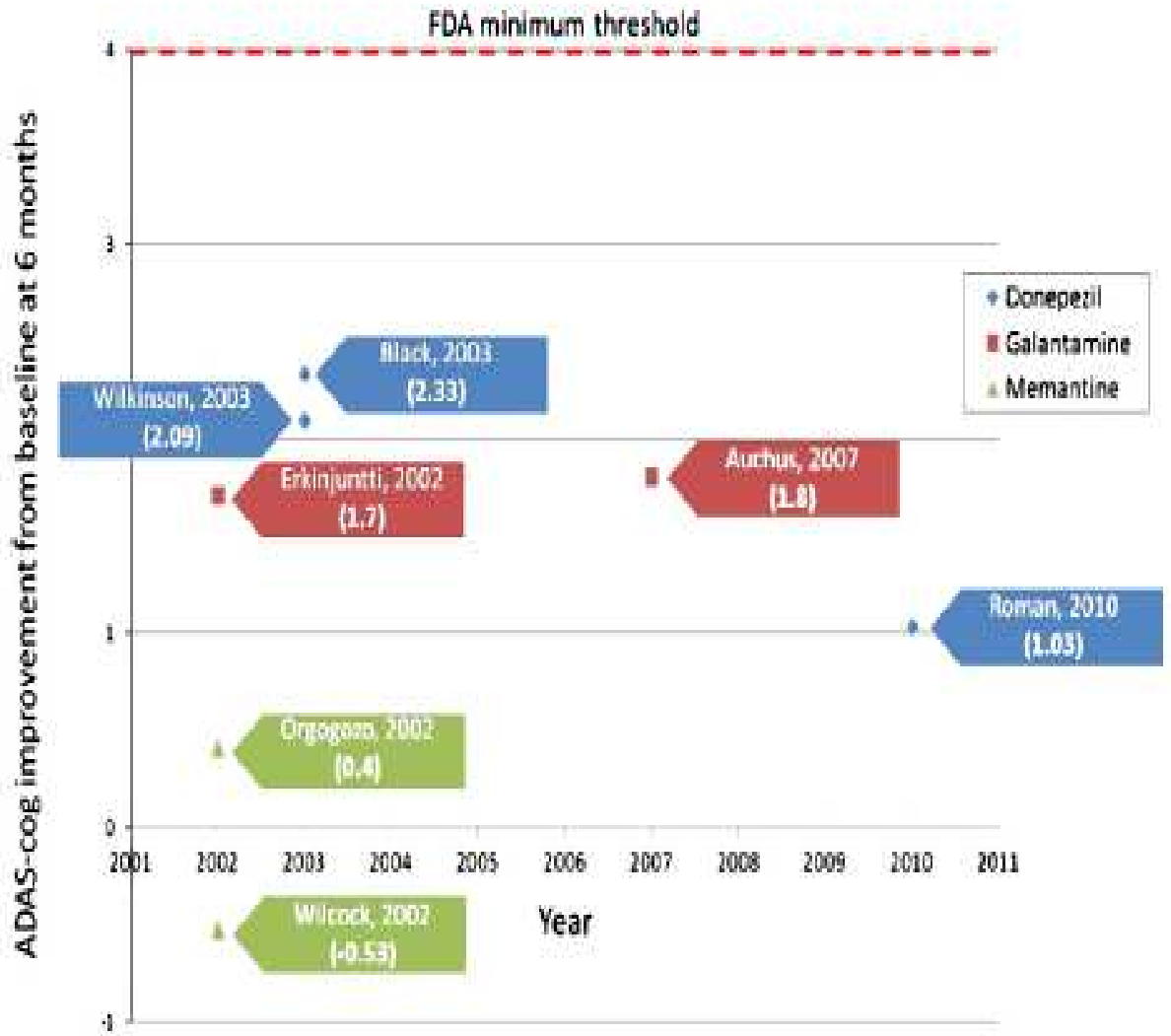


Fig. 1. Change in ADAS-cog score from baseline in vascular dementia trials evaluating the efficacy of AD drugs. Data from Refs. [24–30]. Positive values indicate improvement; negative values indicate worsening.

Farmacocinetica di farmaci anti-demenza

Table 1. Clinical Pharmacology of Agents Useful for Reducing the Signs of Dementia.*

Characteristic	Donepezil	Rivastigmine	Galantamine	Memantine
Time to maximal serum concentration (hr)	3–5	0.5–2	0.5–1	3–7
Absorption affected by food	No	Yes	Yes	No
Serum half-life (hr)	70–80	2†	5–7	60–80
Protein binding (%)	96	40	0–20	45
Metabolism	CYP2D6, CYP3A4	Nonhepatic	CYP2D6, CYP3A4	Nonhepatic
Dose (initial/maximal)	5 mg daily/ 10 mg daily	1.5 mg twice daily/ 6 mg twice daily	4 mg twice daily/ 12 mg twice daily	5 mg daily/ 10 mg twice daily
Mechanism of action	Cholinesterase inhibitor	Cholinesterase inhibitor	Cholinesterase inhibitor	NMDA-receptor antagonist

* CYP2D6 denotes cytochrome P-450 enzyme 2D6, CYP3A4 cytochrome P-450 enzyme 3A4, and NMDA *N*-methyl-D-aspartate.

† Rivastigmine is a pseudo-irreversible acetylcholinesterase inhibitor that has an eight-hour half-life for the inhibition of acetylcholinesterase in the brain.

Cunnings et al, NEJM 2004

Che fare??

… intanto, usarli meglio

……..

Eur J Clin Pharmacol (2006) 62: 721–726
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PHARMACOGENETICS

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Maria Gabriella Scordo · Marja-Liisa Dahl ·
Laura Maria Villa · Aldo Biolcati · Grazia Lombardi

Impact of the *CYP2D6* polymorphism on steady-state plasma concentrations and clinical outcome of donepezil in Alzheimer's disease patients

Abstract *Objective:* The aims of this study were to evaluate the impact of the *CYP2D6* polymorphism on both the steady-state plasma concentrations (Cp) and the clinical outcome of donepezil, a selective acetylcholinesterase inhibitor used in the treatment of Alzheimer's disease (AD). *Methods:* Forty-two patients of Caucasian ethnicity affected by probable AD were included in the study. All had been receiving therapy with donepezil for at least 3 months: 31 patients with 5 mg/day and 11 patients with 10 mg/day. The *CYP2D6* genotype was analysed, and donepezil Cp was measured by using high-performance liquid chromatography. *Results:* On the basis of their *CYP2D6* genotype, 30 patients could be classified as homozygous extensive metabolizers (EM), 10 as heterozygous EM and 2 as ultrarapid metabolizers (UM). No poor metabolizer was found. The dose and body weight-corrected median donepezil Cp were slightly, though not significantly, lower in homozygous than in heterozygous EM (0.33 vs. 0.41 ng/ml/mg/kg, respectively). The latter group consistently showed a better clinical response to treatment, as measured by change in Mini-Mental State Examination score (median: 1.40 vs. −1.30, respectively). UM patients had lower Cp than EM patients and showed no clinical improvement. *Conclusions:* Our preliminary data suggest that the *CYP2D6* polymorphism influences both donepezil metabolism and therapeutic outcome and that a knowledge of a patient's *CYP2D6* genotype together with donepezil concentration measurements might be useful in the context of improving the clinical efficacy of donepezil therapy.

Varsaldi et al, 2006

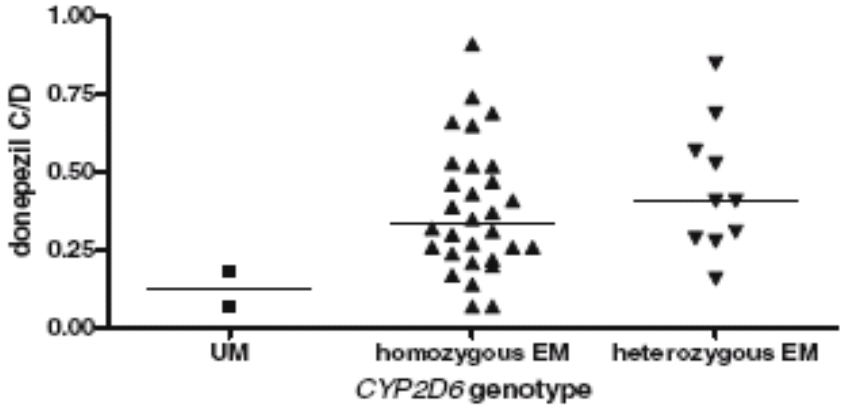


Fig. 1 Relationship between the *CYP2D6* genotype and the plasma concentration-to-dose (C/D) ratios of donepezil (ng/ml/mg/kg). *UM* Ultrarapid metabolizer, defined as a carrier of duplication of a functional gene, *EM homozygous* extensive metabolizer homozygous for the functional *CYP2D6*1* gene, *EM heterozygous* EM heterozygous for a defective *CYP2D6* gene. *Horizontal bars* represent median values

Table 1 Demographic and clinical characteristics of the AD patients and the controls

	AD patients (n=42)	Volunteers (n=48)
Age[a] (years)	61–93 (79±6)	50–80 (60±5)
Male/female (number)	36/6	39/9
Body weight[a] (kg)	39–90	(63±12)
MMSE at baseline[b]	20 (3–28.3)	
MMSE at steady-state[b]	18.2 (7.7–27.7)	
MMSE change −1	(−1.6 to −8.4)	

[a]Data are expressed as range (mean ± SD)
[b]Data are expressed as median (range)

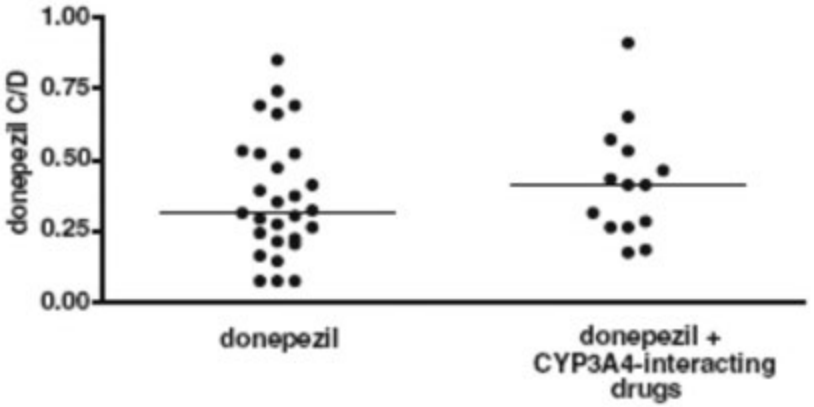
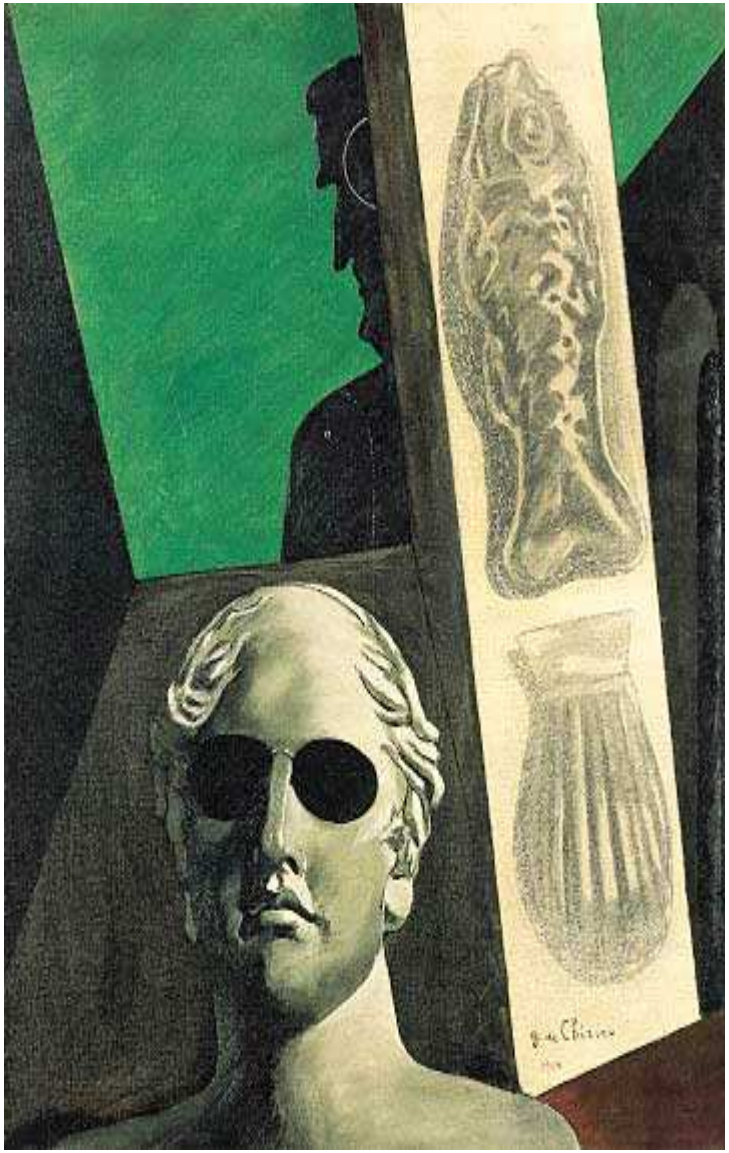


Fig. 2 Relationship between the concomitant administration of CYP3A4-interacting drugs and the plasma concentration-to-dose (C/D) ratios of donepezil (ng/ml/mg/kg). *Horizontal bars* represent median values

Varsaldi et al. 2006



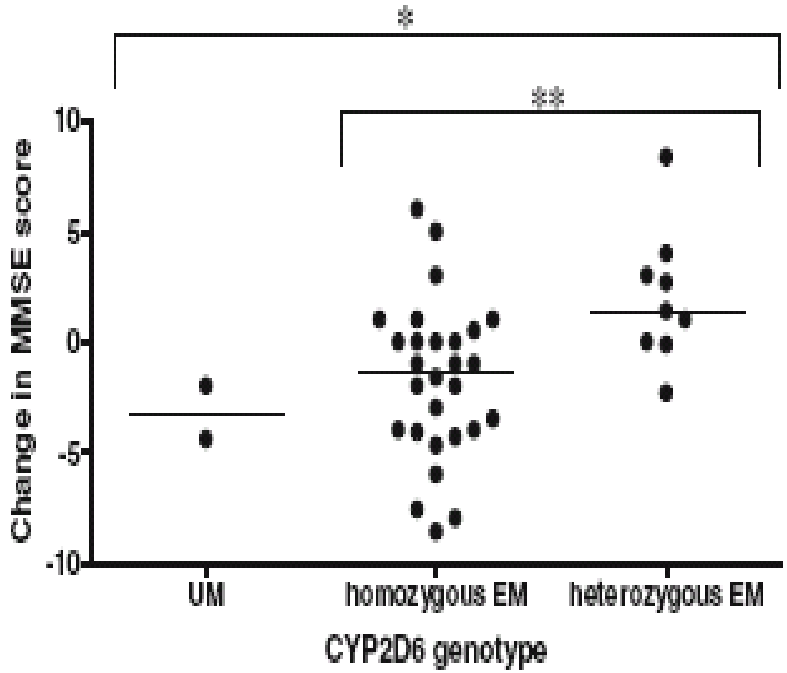


Fig. 3 Relationship between the *CYP2D6* genotype and changes in the MMSE score. *UM* Ultrarapid metabolizer, defined as a carrier of a duplication of a functional gene, *EM homozygous* extensive metabolizer, homozygous for the functional *CYP2D6*1* gene, *EM heterozygous* EM heterozygous for a defective *CYP2D6* gene. *Horizontal* bars represent median values. *$p<0.02$; **$p<0.01$

Varsaldi et al, 2006

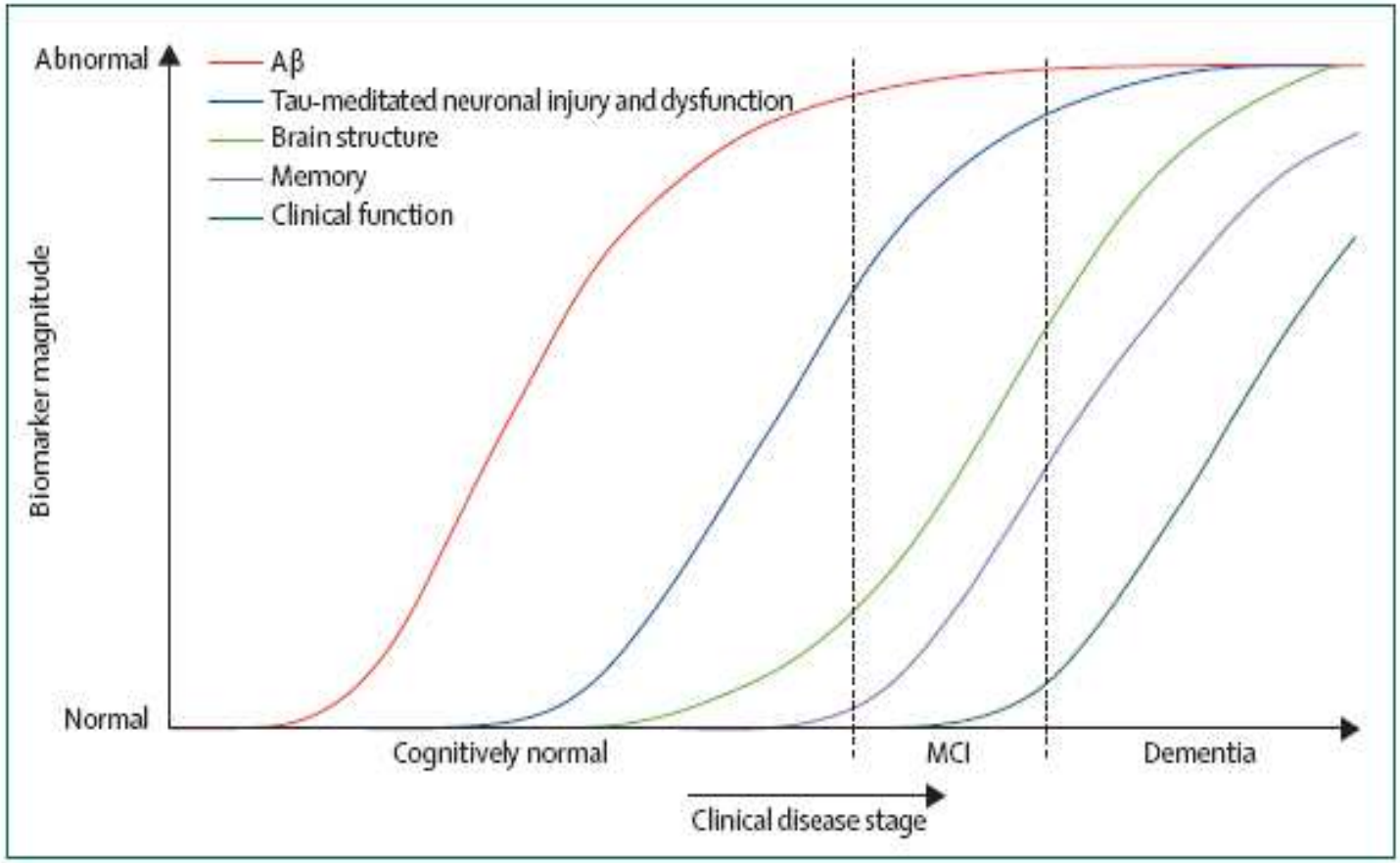


Figure 2: **Dynamic biomarkers of the Alzheimer's pathological cascade**
Aβ is identified by CSF $A\beta_{42}$ or PET amyloid imaging. Tau-mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose-PET. Brain structure is measured by use of structural MRI. Aβ=β-amyloid. MCI=mild cognitive impairment.

JACK, Lancet Neurol 2010

Table 1. List of drugs approved for treatment of AD and potential new classes of compounds that have been or that will be included in clinical trials.

Current symptomatic treatment for AD	
Acetylcholinesterase inhibitors	donepezil
	rivastigmine
NMDA antagonist	memantine
Novel pharmacological approaches targeting Aβ and tau	
α-secretase activators	
β-secretase inhibitors	
γ-secretase inhibitors	
γ-secretase modulators	
aggregation inhibitors	
active Aβ immunotherapy	
passive Aβ immunotherapy	
microtubule stabilizers	
kinase inhibitors	
aggregation inhibitors	
activators of tau clearance	

ALZHEIMER: amiloidogenesi

Accumulo di beta-amiloide

↓

Attivazione di astrociti e microglia

↓

Danno ossidativo, alterazione dell'omeostasi

↓

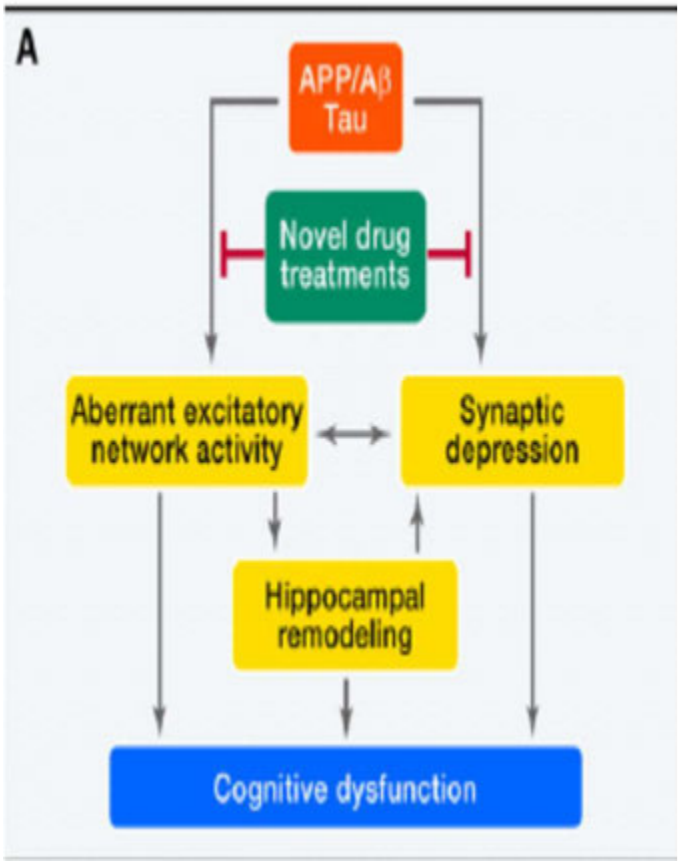
Deficit sinaptico e neuronale

↓

Morte neuronale

↓

DEMENZA



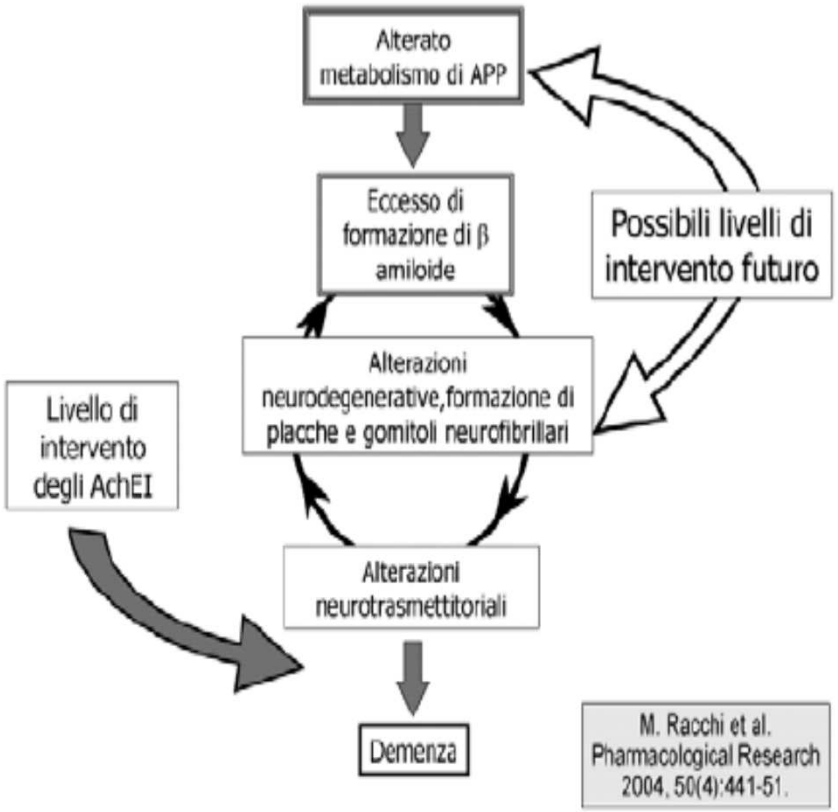


Fig. 2. Cascata patogenetica per la malattia di Alzheimer: collocazione dell'intervento sintomatico (AchEI) e dei possibili interventi *"disease modifying"*. Nella malattia di Alzheimer le alterazioni del metabolismo della proteina precursore di beta-amiloide (APP) porterebbero alla formazione di eccesso ed accumulo di beta-amiloide. Tale peptide, secondo l'ipotesi qui discussa, sarebbe responsabile delle alterazioni biochimiche e neurochimiche con conseguente sviluppo e manifestazione clinica dei sintomi della demenza. I farmaci oggi disponibili come gli AchEI, aumentano le concentrazioni di acetilcolina intervenendo sulla sintomatologia. Lo sviluppo di nuovo farmaci ha come obiettivo di intervenire anche ad altri livelli compresa la formazione di beta amiloide (da Perry et al, 2005 [4], mod.).

L'ipotesi Beta-Amiloide

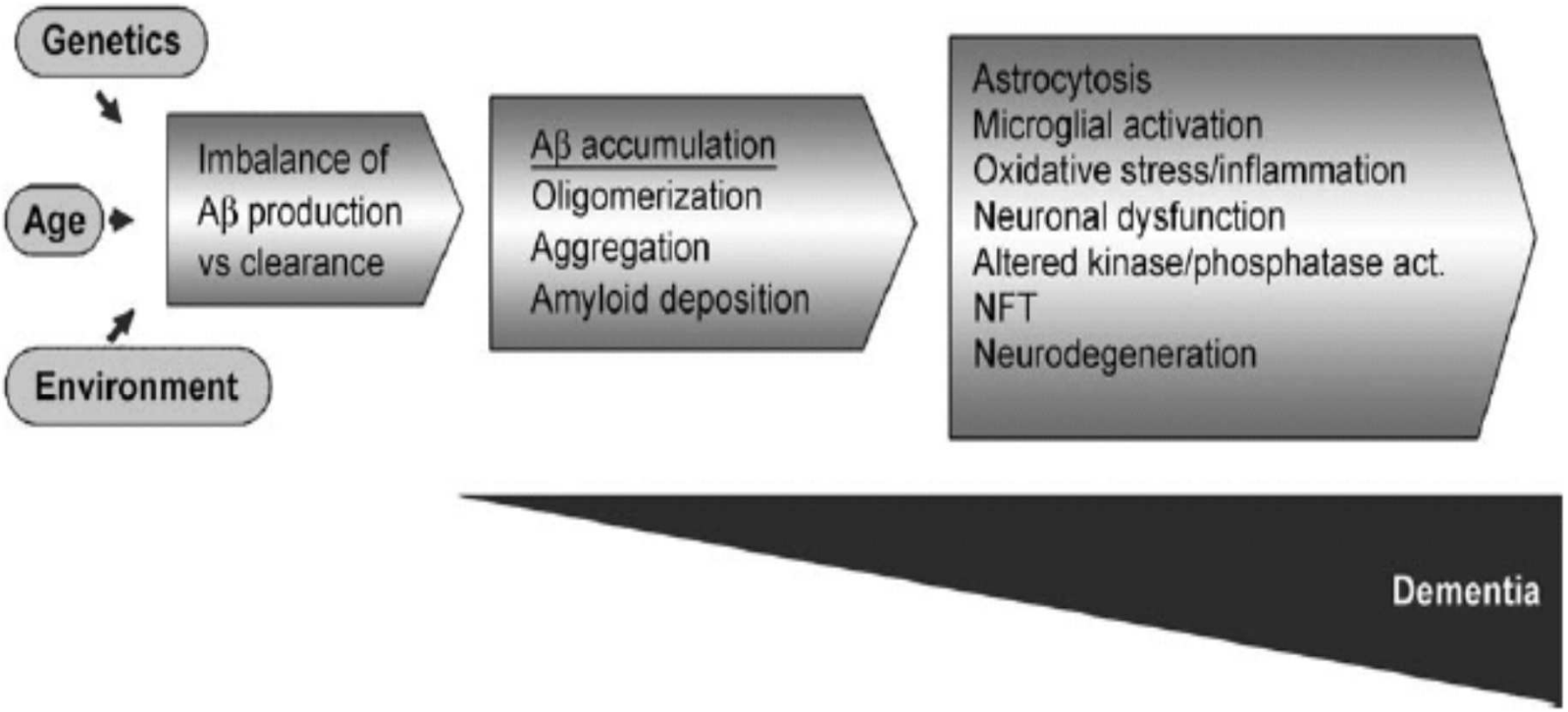


Figure 8. The amyloid cascade hypothesis of Alzheimer's disease.

La cascata della Proteina Beta-Amiloide

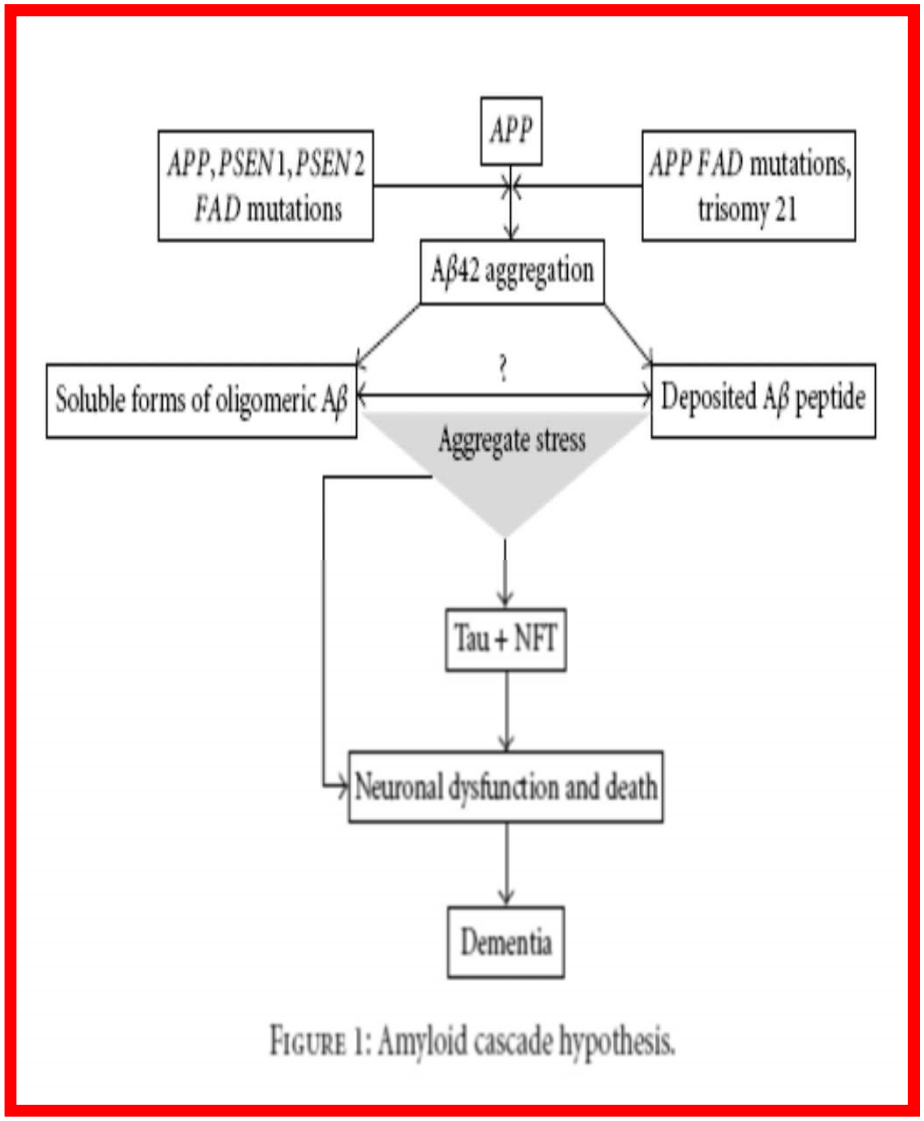


FIGURE 1: Amyloid cascade hypothesis.

Al momento, non ci sono farmaci in grado di prevenire, arrestare o revertire la demenza di Alzheimer.

Intensa ricerca negli ultimi 20 anni, tutta incentrata su Aβ e Tau

Risultati clinici, però, sono assai deludenti

1. Inibire la produzione di Aβ: modulare le secretasi

- inibitori e modulatori di γ-secretasi
- inibitori di β-secretasi
- stimolanti di α-secretasi

2. Prevenire l'aggregazione di amiloide (Tramiprosoate, colostrinin)

3. Rimuovere l'amiloide, attivando enzimi di degradazione (ad es., RAGE)

4. Immunizzazione attiva: vaccini

5. Immunizzazione passiva: infusione di anticorpi anti-Aβ in pazienti (bapineuzumab, solanezumab)

SECRETASI

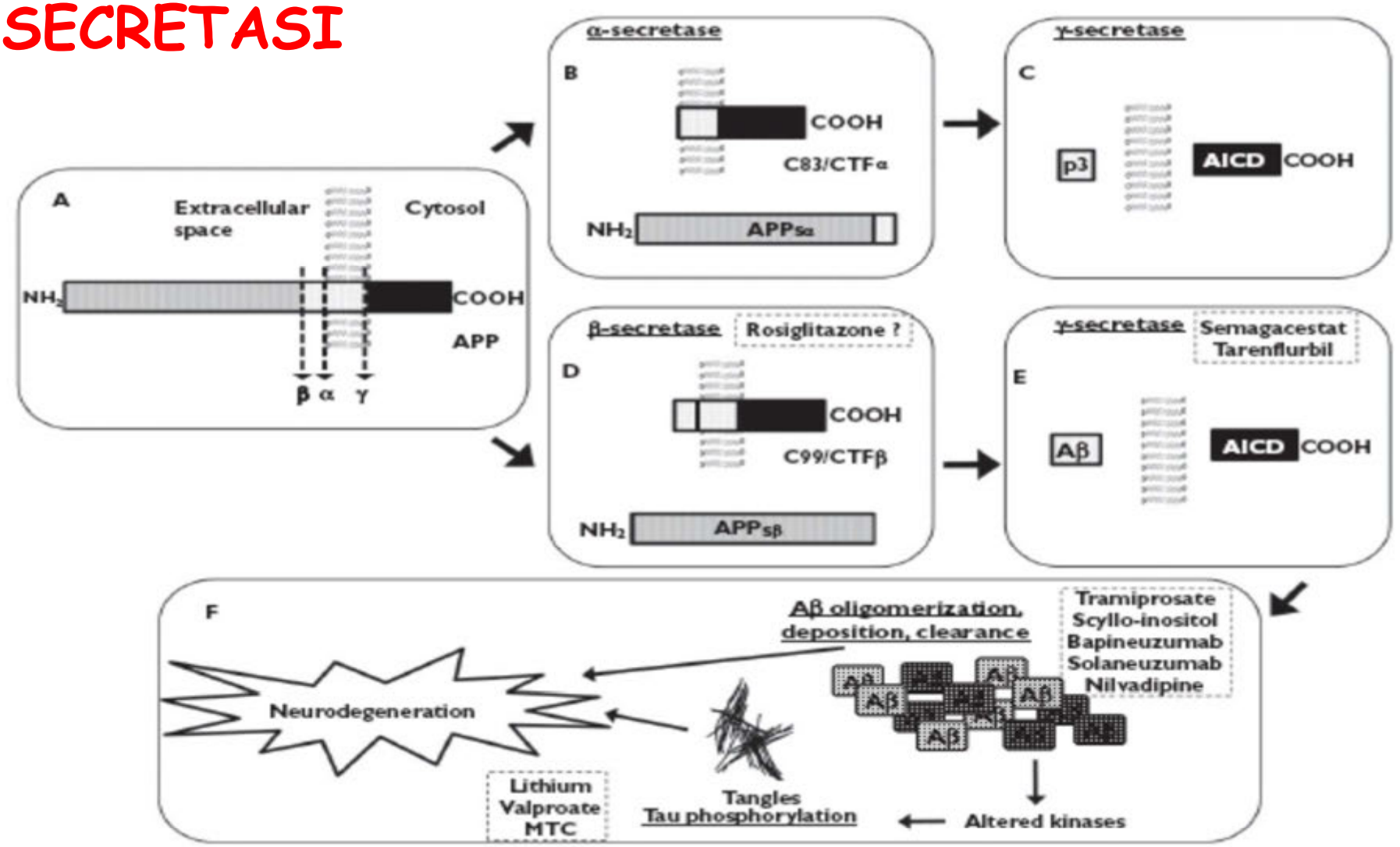


Figure 1

Main steps of sequential cleavage of amyloid precursor protein (APP), leading to generation of β amyloid (Aβ) and/or other products. In A, dashed arrows indicate the cleavage sites for α-, β- and γ-secretase. In B, ectodomain shedding of APP by α-secretase gives a soluble extracellular APP fragment (APPsα) and a 83 amino acid, membrane-bound, carboxy terminus fragment (C83/CTFα). Subsequent intramembrane proteolytic cleavage of C83/CTFα by γ-secretase (in C) releases a short extracellular p3-peptide (p3) and a cytosolic APP intracellular domain (AICD). In D, ectodomain shedding of APP by β-secretase gives a soluble extracellular APP fragment (APPsβ) and a 99 amino acid, membrane-bound, carboxy terminus fragment (C99/CTFβ). Subsequent intramembrane proteolytic cleavage of C99/CTFβ by γ-secretase (in E) releases extracellular Aβ and a cytosolic APP intracellular domain (AICD). In F, Aβ oligomerization and deposition lead to neurodegeneration, both directly and through tau hyperphosphorylation. In dashed boxes, disease modifying drugs that interfere with each particular step. See text for more information and references

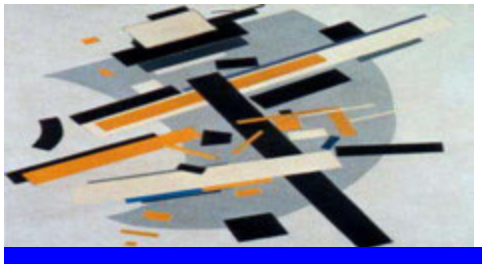
Salomone et al, 2011

γ-secretasi: inibitori e modulatori

1. **Inibizione di γ-secretasi è stato il primo target;** nel 2001 si è visto che inibizione di questo enzima riduce, in vivo, la produzione di Aβ

2. **Tuttavia, nell'animale, gravi effetti collaterali** (enteropatia mucosa gastrointestinale, anormale differenziamento dei linfociti), perché questo enzima è una proteasi che cliva diversi substrati (tra cui Notch receptor protein) oltre ad APP.

3. **Da qualche tempo, interesse è soprattutto per inibitori selettivi o modulatori di γ-secretasi**



Inibitori di γ-secretasi

Semagestat (LY450139): inibitore non selettivo. In fase I, nel volontario sano, ha < livelli plasmatici di Aβ, ma non quelli in liquor, ed è stato abb ben tollerato. Anche in studi di fase II, in pazienti AD mild-moderate, < livelli plasmatici, ma non quelli in liquor; effetti indesiderati gastrointestinali e dermatologici. Poi, 2 studi multicentrici di Fase III (IDENTITY e IDENTITY-2) per valutare efficacia e sicurezza di 140 mg di semagestat in 2000 paz AD: arruolamento non completato perché, a interim analysis, **i paz trattati avevano peggiori valori cognitivi e funzionali e > rischio di tumore cutaneo rispetto al placebo**

Tarenflurbil (Flurizan, MPC-7869): R-enantiomero del flurbiprofen che, in animali transgenici, < accumulo di Aβ in placca e migliora memoria e performances. In fase I, ben tollerato ma non < $A\beta_{42}$ in plasma o liquor. In fase II, prolungata, paz trattati per 2 anni, hanno < deficit cognitivo di placebo. Studio di fase III in 1649 paz AD mild-moderate (800 md/b.i.d): **nessun vantaggio cognitivo**

BMS-708163: inibitore selettivo, non degrada Notch. Attualmente in fase III

Begacestat (GSI-935): derivato sulfonamidico che < Aβ42, ottimi effetti in topo transgenico. In un solo studio in uomo, < i livelli plasmatici di Aβ.

Table 1 γ-Secretase inhibitors in clinical development for the treatment of Alzheimer's disease (AD)

Compound	Mechanism of action	Side effects	Development status	Company	References
Semagacestat (LY-450139)	Decreases newly synthesized Aβ in CSF of AD patients	No significant effects on brain plaque burden in transgenic mice. Lack of data on behavioral effects in animal models of AD. Gastro-intestinal and skin side effects in AD patients	Phase III	Eli-Lilly	[42]
MK-0752	Decreases Aβ40 levels in CSF of healthy volunteers	Inhibits Notch cleavage. Significant gastro-intestinal toxicity in humans	Abandoned[a]	Merck	[43]
E2012	Notch sparing	Lenticular opacity in rats	Phase I	Eisai	[40]
BMS-708163	Notch sparing Decreases Aβ levels in CSF of healthy volunteers	Lack of data on brain plaque deposition in transgenic mice. Lack of data on behavioral effects in animal models of AD	Phase II	Bristol Myers Squibb	[44]
PF-3084014	Notch sparing. Good brain penetration. Long-lasting effects on Aβ levels in animals. No rebound effect on plasma Aβ in animals	Lack of data on brain plaque deposition in transgenic mice. Lack of data on behavioral effects in animal models of AD	Abandoned[a]	Pfizer	[45]
GSI-953 (begacestat)	Improves memory in a transgenic mouse model of AD.	Does not decrease Aβ40 levels in CSF of AD patients	Phase II	Wyeth	[46]

[a] In development as anticancer agent.
Aβ, β-amyloid; CSF, cerebrospinal fluid.

Panza et al, 2010

Inibitori di β-secretasi

Enzima cruciale nel metabolismo di amiloide; in uomo ci sono 2 enzimi: BACE1 (quello più importante per amiloide) e BACE2. **Animali BACE1-ko non producono Aβ.** Tuttavia, vari problemi per mettere a punto inibitori efficaci. Infatti, BACE1, oltre ad amiloide, cliva anche neuregulina 1 (NRG1: importante per mielinizzazione periferica).

Per la struttura molecolare di BACE1, gli inibitori sono grossi e idrofilici (problema di farmacocinetica, passaggio della BEE, possibile scarsa efficacia terapeutica).

Vari composti sono stati valutati per superare questi ostacoli,ma, finora, non c'è alcun valido candidato.

Stimolazione di α-secretasi

Stimolazione di questo enzima < APP disponibile per cascata amiloide e porta a formazione di frammenti solubili (saAPP), che hanno un ruolo neuroprotettivo e stimolano sinaptogenesi.

Questi enzimi appartengono a famiglia ADAM (A Disintegrin And Metalloproteinase). La iperespressione di ADAM 10 in animale transgenico > sinaptogenesi colinergica, migliora aspetto cognitivo e previene il deposito di beta-amiloide nella placca.

Carbacolo ed agonisti muscarinici M1 e M3 stimolano l'attività di α-secretasi

Esteri del forbolo (attivatore diretto di PKC), **agonisti 5-HT4, stimolanti MAPK e PI-3K, stimolano l'attività di α-secretasi**

2. PREVENIRE L'AGGREGAZIONE DI AMILOIDE

Varie specie di amiloide sono normalmente presenti in cervello umano; la loro semplice presenza non porta a neurodegenerazione

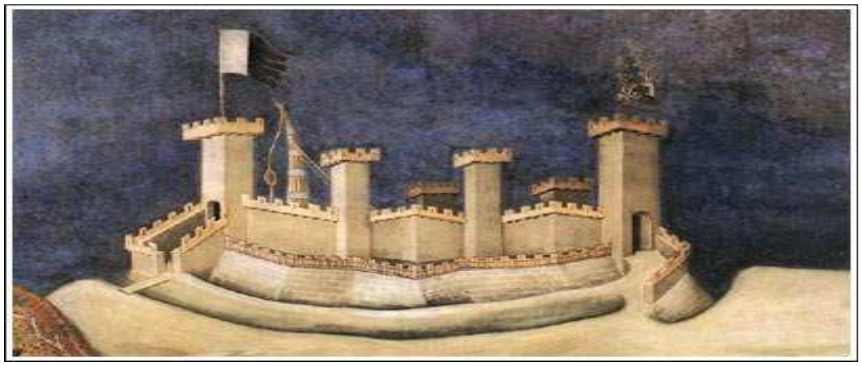
Per avere neurodegenerazione, è necessaria l'aggregazione di Aβ a formare oligomeri, fibrille e neurofibrille, e poi deposizione nelle placche amiloidi

Anti-aggreganti di Amiloide

- Tramiprosoate
- Colostrinin
- Metal protein attenuating compounds: PBT1 (Cloquinol) e PBT2
- Scyllo-inositol (ELND005, prima AZD103)

Tramiprosoate

Mimetico di glusosaminoglicano (GAG). GAGs legano Aβ solubile, promuovendo formaz fibrille e deposiz in amiloide



I GAG-mimetici prevengono la formazione di fibrille e < Aβ solubile, competendo per GAG-binding sites.

In animali transgenici, Tramiprosoato < placca e livelli cerebrali di Aβ.

In fase I: ben tollerato.

Fase II della durata di 3 mesi: < livelli Aβ42 (fino a 70%), ma non differenze significative rispetto al placebo, a livello cognitivo

Fase III in USA e Canada, 1052 pazienti AD mild-moderate: **nessun significativo vantaggio a livello cognitivo**

Colostrin: presente in colostro. < aggregazione di Aβ e migliora cognizione in modelli animali. Tollerato in fase I, modesto miglioramento cognitivo in fase II nei primi 15 mesi, ma non dopo

PBT1-Cloquinol: ruolo possibile di rame e zinco, assieme ad amiloide, nel produrre aggregazione di Aβ. E' un vecchio chinolonico che inibisce legame di rame e zinco ad Aβ, inibendo aggregazione. Ritirato dal mercato, come chinolonico, per neuropatia ottica. In piccolo studio clinico, < declino cognitivo in paz AD moderate-severe.

PBT2: derivato dal precedente. In fase II, 250 mg/die per 12 settimane: < Aβ42 in liquor.

Scyllo-inositol: inibisce aggregaz di Aβ42, formando un composto non tossico. Studio di fase II, 18 mesi, non raggiunge significatività statistica per parametri cognitivi (cadute, depressione e confusione come effetti avversi).

3. RIMOZIONE dell'AMILOIDE

Teoricamente: attivazione degli enzimi di degradazione, aumentare il suo trasporto dal cervello alla periferia, o rimozione diretta attraverso risposta immunologica

I più importanti **enzimi della degradazione** sono: neprilisina, insulin-degrading enzymes, plasmina.

Trasporto di Aβ nel cervello è mediato da RAGE (receptor for advanced glycation end product): RAGE-inibitore sviluppato da Pfizer (tollerato, ma non miglioramento cognitivo).

Trasporto di Aβ da cervello a periferia è mediato da LRP-1 (low-density lipoprotein receptor-related protein)

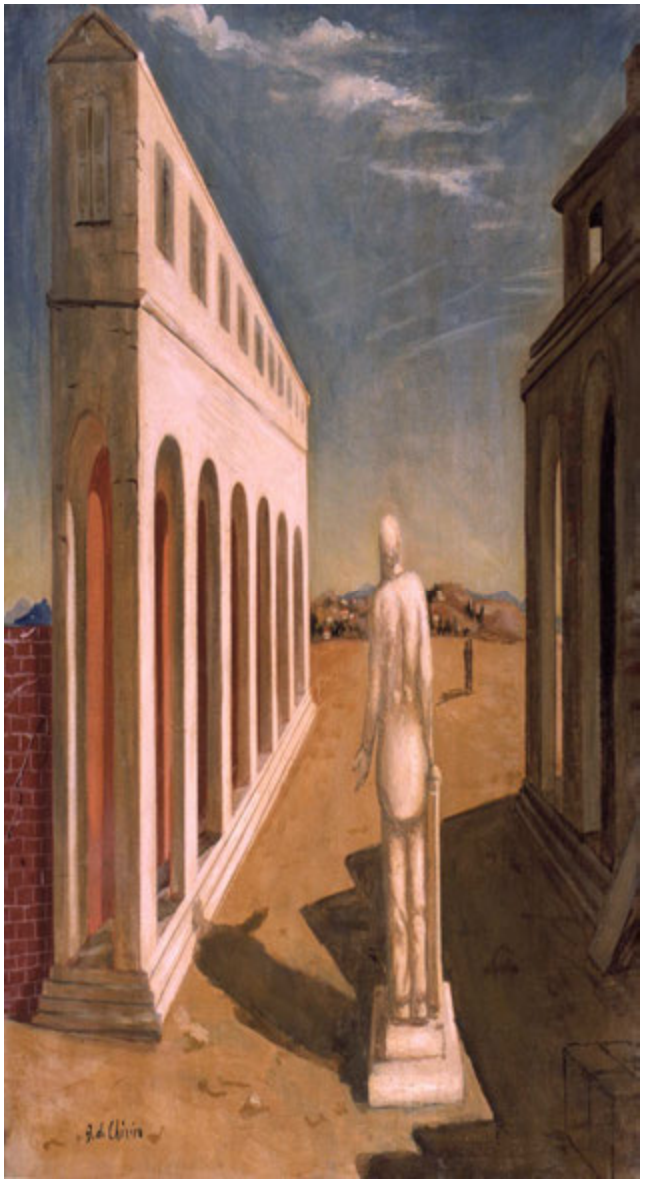
Immunoterapia: attiva (vaccini) e passiva

VACCINI

Prima generazione: AN1792. Fase I con 80 paz AD mild-moderate. Oltre 50% ha risposta anticorpale, ma 25% effetti indesiderati importanti. Studio di fase II: 300 pazienti con AD: **meningoencefalite asettica** nel 6% dei casi (studio bloccato). Risultati analoghi con altro vaccino, **QS-21.** In questo studio, 20 paz vaccinati mostrano un più lento declino cognitivo e delle attività quotidiane.

Seconda generazione: CAD106 (Novartis) peptide N-terminale (Aβ 1-6) più corto, così da favorire risposta umorale piuttosto che cellulare (come con quelli di prima generazione, più lunghi: a ciò è stata attribuita la meningite). Studio di fase I: vaccino sicuro e ben tollerato. Lo studio di fase II è in corso.

IMMUNIZZAZIONE PASSIVA



In animale, infusione passiva di ATC può portare a degradazione delle placche

Bapineuzumab: monoclonale umanizzato che lega con alta affinità Aβ 1-5, specie se Aβ è depositata nelle placche senili. Fase I OK. Fase II: 234 paz, 1-6 dosi e.v. ogni 13 sett. Effetto migliore in APOE 4 non-carriers. Edema reversibile vasogenico come effetto collaterale. Studi di fase III, separati per ApoE carrirs e non-carriers: sarà completato nel 2016. Inoltre, lo si sta provando anche s.c.

Solaneuzumab: monoclonale umanizzato diretto contro epitopi al centro di Aβ (Aβ 13-28); lega meglio forme solubili e agisce soprattutto su Aβ periferica. Fase I OK. Fase II: ben tollerato, ma non variazioni nei markers valutati. In corso, 2 trials di fase III (EXPEDITION 1 e 2).

Terapie dirette su proteina Tau

Tau è proteina associata a microtubulo che viene abnormemente **iperfosforilata**, si aggrega e accumula nei neuroni, formando le **neurofibrille**, e porta a **morte neuronale**

• **Tau anti-aggreganti. MTC** (metiltionino cloruro) è agente riducente, meglio noto come **blu di metilene**. Studio di fase II contro placebo: rallentamento di progressione di AD di circa 80%. In corso, studio per dose-ranging.

• **Inibitori di iperfosforilazione di Tau: litio**. GSK-3β (glicogenosintasi kinasi 3β) è principale mediatore di iperfosforilazione di tau. In animale, il litio < livelli di tau iperfosforilata ed espressione di GSK-3 in corteccia. **Studio caso-controllo in paz bipolari trattati con litio**, ha mostrato che hanno un **rischio di sviluppare AD entro 6 anni significativamente ridotto** rispetto a controlli di pari età che non assumono litio.

Disease-modifying drugs for Alzheimer's disease BJCP

Current status of clinical development of some disease modifying drugs for treatment of Alzheimer's disease (AD)

Drug	Mechanism of action relevant for AD	Phase of study	Result of study	Caveat of study
Rosiglitazone	β-secretase inhibition (?)	3	Ineffective	Lack of biomarker
Semagacestat	γ-secretase inhibition	3	Premature end	Severe adverse drug reaction
Tarenflurbil	γ-secretase modulation	3	Ineffective	Low potency, blood–brain barrier passage
Tramiprosate	Inhibition of Aβ oligomerization	3	Ineffective	–
Scyllo-inositol	Inhibition of Aβ oligomerization	2	Ineffective	Biomarker change
Bapineuzumab	Aβ clearance	3	Ongoing	Vasogenic oedema, amyloid angiopathy
Solaneuzumab	Aβ clearance	3	Ongoing	–
Lithium	Inhibition of tau phosphorylation	2	Clinical improvement Decrease of P-tau in CSF	–
Methylthioninium chloride	Inhibition of tau aggregation	2	Clinical improvement with 60 mg day^{-1}	Lack of biomarker
Nilvadipine	Aβ clearance	Open label	Clinical improvement	Lack of biomarker
Latrepirdine	Mitochondrial protection	3	Ineffective	–
		3	Ongoing (in association with other drugs)	–

Salomone et al, 2011

Anti-infiammatori e neuroprotettori

FANS. Studi epidemiologici suggeriscono che uso cronico di FANS protegge da sviluppo di AD. **Effetto protettivo dipende da durata trattamento e genotipo ApoE** (solo quelli con allele ApoEε4 hanno protezione), beneficio solo in fase prodromica o molto iniziale di AD. Indometacina, COX-2 inibitori, naproxen. Problemi di tollerabilità e sicurezza. Studio ADAPT (prevenzione primaria) sospeso per eventi cardiovascolari.

Statine. Vari studi ad hoc (CLASP, PROSPER, LEADe). Non c'è alcun vantaggio a livello cognitivo e funzionale

Vitamine e antiossidanti. Vit B12, ac. Folico, Vit. D, Vit E, C e beta-carotene. Studi epidemiologici, ma nessun effetto certo.

CONSIDERAZIONI

- Con terapia attualmente disponibile, circa il 50% dei pazienti presentano una insufficiente risposta terapeutica

- E' indispensabile lo sviluppo di nuovi farmaci, terapie alternative e/o co-somministrabili

Review

Alzheimer's disease: brain expression of a metabolic disorder?

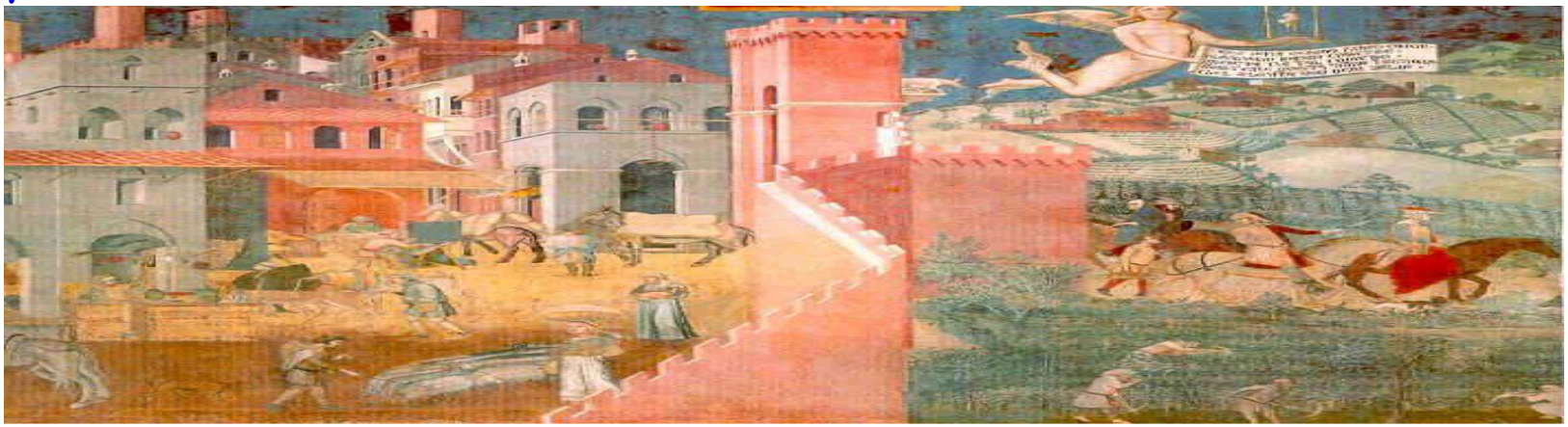
Sara Merlo[1], Simona Spampinato[1], Pier Luigi Canonico[2], Agata Copani[3] and Maria Angela Sortino[1]

Alzheimer's disease (AD) is the most common form of dementia and is of rapidly increasing health, social and economic impact. Recent evidence suggests a strict link between metabolic disorders and AD. In the last decade much attention has focused specifically on the connection between dysfunction of lipid metabolism and AD. Here we discuss aspects of lipid regulation, including changes in cholesterol levels, function of apolipoproteins and leptin, and how these relate to AD pathogenesis. Despite the vast literature available, many aspects still need clarification. Nevertheless, the route is already delineated to directly connect aspects of lipid regulation to AD. This could represent a starting point to identify novel potential targets for a preventive and/or treatment strategy of the disease.

Serum cholesterol, triglycerides, HDL and LDL in aggressive elderly patients with dementia

Scheffel A, *Psychiatr Pol. 1996 Jan-Feb;30(1):159-70*

Associations were analysed between serum concentrations of cholesterol, triglycerides, HDL and LDL measured after hospital admission, and physical aggression in a sample of elderly patients with dementia (210 women and 160 men). A significant lower serum cholesterol and LDL concentration were found in aggressive patients of both sexes and a significant lower serum triglycerides only in aggressive women. In the subgroups of Alzheimer type dementia, women showed significant lower serum triglycerides



High total cholesterol levels in late life associated with a reduced risk of dementia

Mielke et al, Neurology 2005;64:1689-95

High cholesterol in late life was associated with decreased dementia risk, which is in contrast to previous studies suggesting high cholesterol in mid-life is a risk factor for later dementia. The conflicting results may be explained by the timing of the cholesterol measurements in relationship to age and the clinical onset of dementia.

Alzheimer e metabolismo lipidico

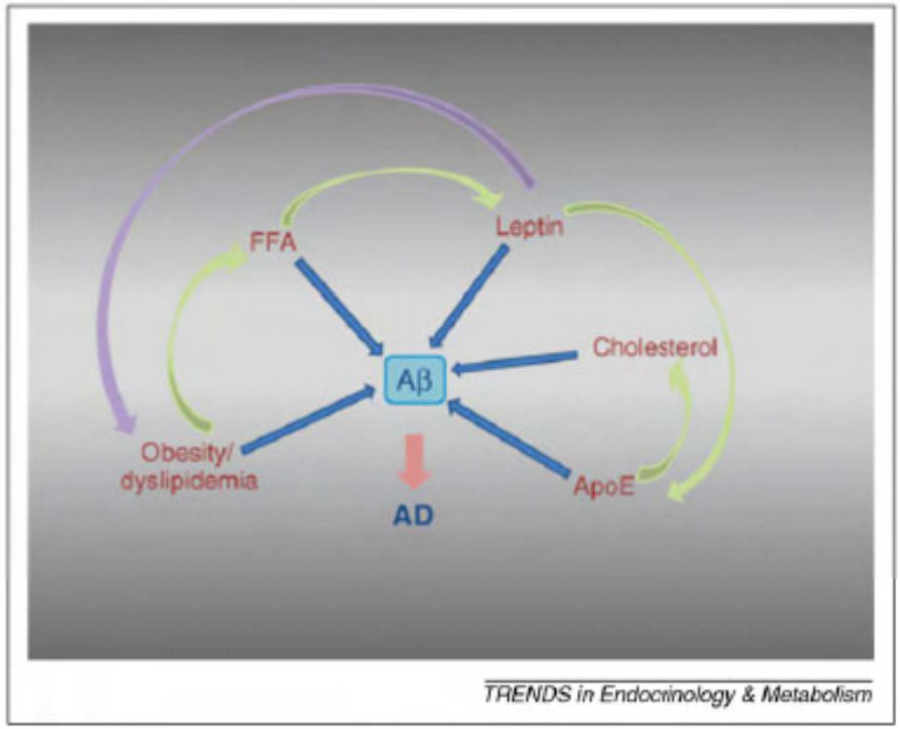


Figure 1. AD and its relationship with lipid metabolism. Each player and/or regulator of lipid metabolism intervenes independently on AD pathogenesis mainly by modifying synthesis and/or clearance of Aβ, the main constituent of senile plaques. High cholesterol and FFA are associated with increased Aβ load, due to increased synthesis and/or altered clearance. The same occurs under dyslipidemic conditions, and mid-life obesity is often a feature of patients who will develop AD. APOE, depending on its lipidation state, significantly modifies Aβ clearance, but effects of APOE on Aβ aggregation cannot be ruled out. By contrast, the adipokine leptin negatively controls Aβ synthesis while facilitating its clearance. Therefore, targeting each of these factors appears promising to obtain changes of Aβ accumulation. The multiple links existing among all these lipid metabolism regulators (indicated by arrows) suggest that interventions at each level could provide not only a direct effect on Aβ, but also a more global indirect regulatory action that will probably participate in the final response.

Box 3. Outstanding questions

- What makes *APOE4* a risk factor for neurodegenerative diseases other than AD? What is the relevance of Aβ-independent actions of APOE? How can APOE be targeted to control Aβ accumulation?
- What is the real efficacy of statins in treating and/or preventing AD? Does their effectiveness depend on the type of drug utilized, on the severity of and/or time of intervention in AD? What is the mechanism of action of statins in protecting neurons against Aβ toxicity?
- Could changes in peripheral leptin concentrations be predictive of AD? Is it time to design clinical trials based on the preclinical findings that inversely correlate leptin levels to AD?

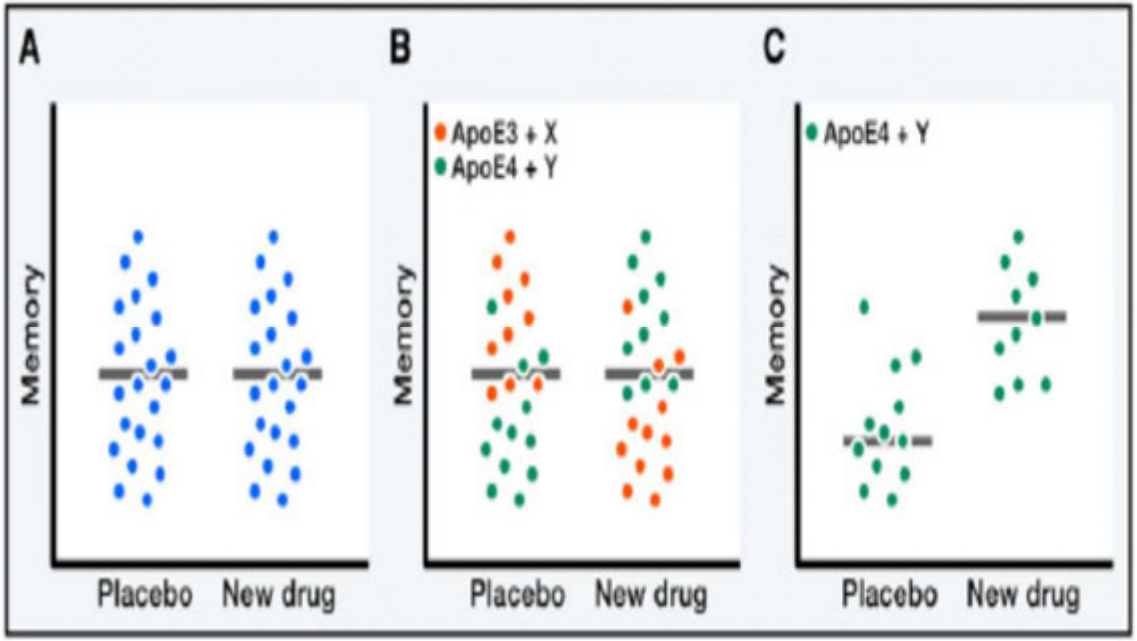


Figure 5. Impact of Patient Heterogeneity and Modifier Genes on Drug Trials

Hypothetical data clouds with dots representing memory measures obtained in individual human subjects.

(A) Without better preselection of patients, potentially effective new drugs may show no efficacy in clinical trials because of the heterogeneity of the patient population tested.

(B and C) Stratification of patient populations based on measurements of biomarkers and identification of specific genes could help match up subpopulations with the most suitable drug and significantly increase the chances of identifying better treatments for AD and related disorders.

ApoE, selezione pazienti e trial clinici

Huang & Mucke, Cell 2012

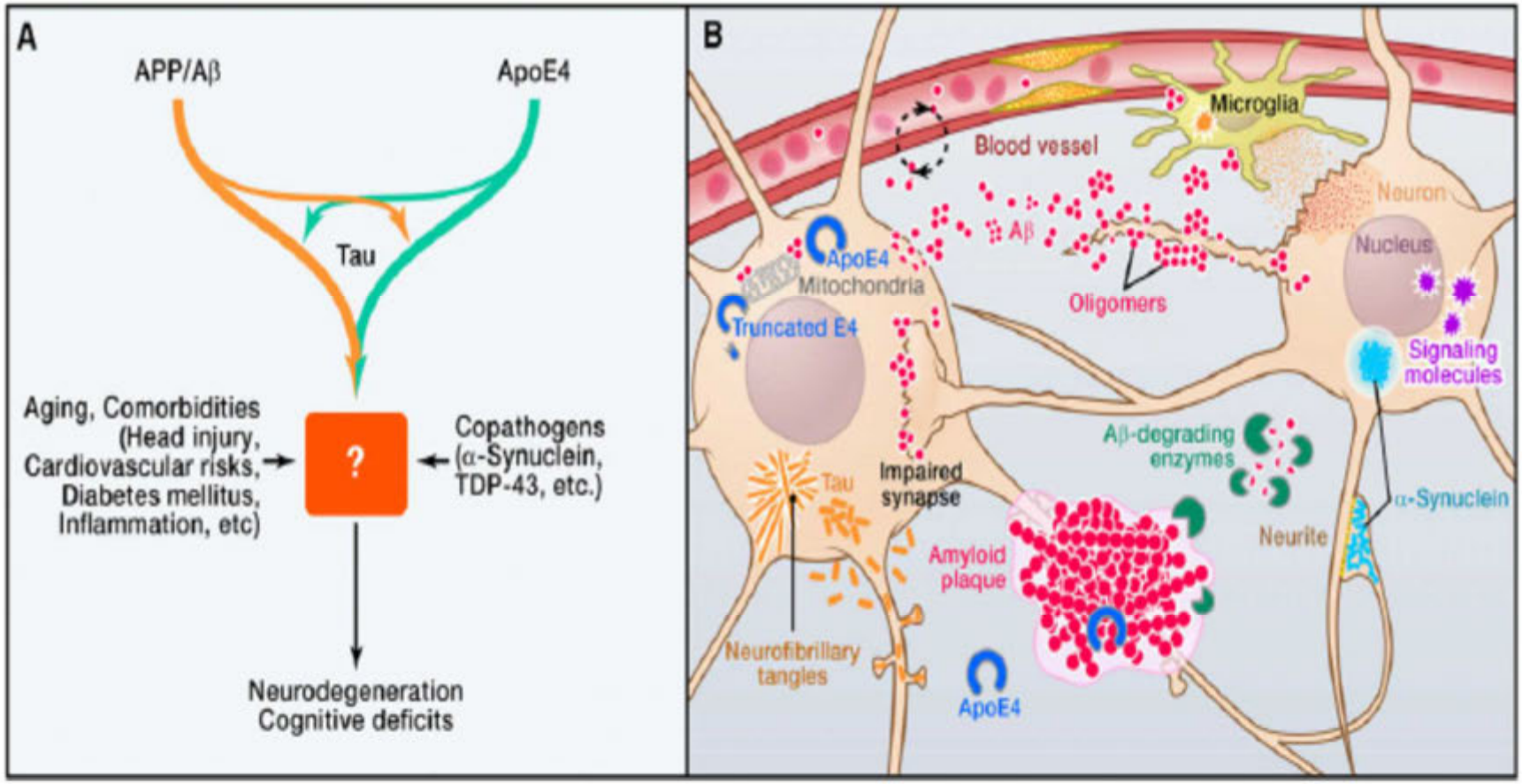


Figure 1. Multifactorial Basis of Alzheimer's Disease Pathogenesis

(A) Alzheimer's disease (AD) is likely to be caused by copathogenic interactions among multiple factors, including APP/Aβ, apoE4, tau, α-synuclein, TDP-43, aging, and various comorbidities. How exactly they conspire to impair neuronal functions and survival remains to be determined.

(B) Aggregation and accumulation of Aβ in the brain may result from increased production of Aβ, decreased degradation by Aβ-degrading enzymes, or reduced clearance across the blood-brain barrier. Aβ oligomers impair synaptic functions and related signaling pathways, changing neuronal activities, and trigger the release of neurotoxic mediators from glial cells. Fibrillar amyloid plaques displace and distort neuronal processes. The lipid transport protein apoE4 impairs Aβ clearance and promotes Aβ deposition. When expressed within stressed neurons, apoE4 is cleaved, to a much greater extent than apoE3, into neurotoxic fragments that disrupt the cytoskeleton and impair mitochondrial functions. Tau, which is normally most abundant in axons, becomes mislocalized to the neuronal soma and dendrites and forms inclusions called neurofibrillary tangles (NFTs). α-synuclein can also self-assemble into pathogenic oligomers and form larger aggregates (Lewy bodies). Both tau and α-synuclein can also be released into the extracellular space, where they may spread to other cells. Vascular abnormalities impair the supply of nutrients and removal of metabolic byproducts, cause microinfarcts, and promote the activation of glial cells.

Docosahexaenoic Acid Supplementation and Cognitive Decline in Alzheimer Disease

A Randomized Trial

Context Docosahexaenoic acid (DHA) is the most abundant long-chain polyunsaturated fatty acid in the brain. Epidemiological studies suggest that consumption of DHA is associated with a reduced incidence of Alzheimer disease. Animal studies demonstrate that oral intake of DHA reduces Alzheimer-like brain pathology.

Objective To determine if supplementation with DHA slows cognitive and functional decline in individuals with Alzheimer disease.

Design, Setting, and Patients A randomized, double-blind, placebo-controlled trial of DHA supplementation in individuals with mild to moderate Alzheimer disease (Mini-Mental State Examination scores, 14-26) was conducted between November 2007 and May 2009 at 51 US clinical research sites of the Alzheimer's Disease Cooperative Study.

Intervention Participants were randomly assigned to algal DHA at a dose of 2 g/d or to identical placebo (60% were assigned to DHA and 40% were assigned to placebo). Duration of treatment was 18 months.

Main Outcome Measures Change in the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) and change in the Clinical Dementia Rating (CDR) sum of boxes. Rate of brain atrophy was also determined by volumetric magnetic resonance imaging in a subsample of participants (n = 102).

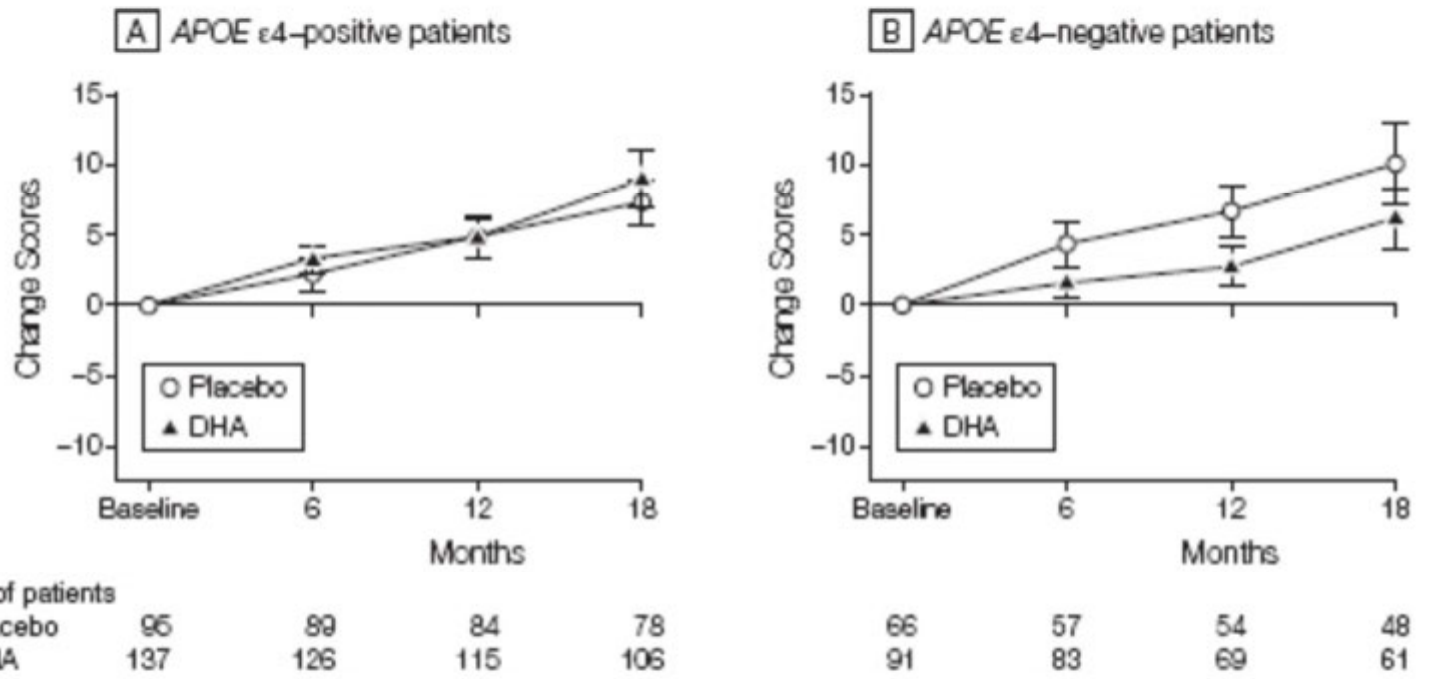
Results A total of 402 individuals were randomized and a total of 295 participants completed the trial while taking study medication (DHA: 171; placebo: 124). Supplementation with DHA had no beneficial effect on rate of change on ADAS-cog score, which increased by a mean of 7.98 points (95% confidence interval [CI], 6.51-9.45 points) for the DHA group during 18 months vs 8.27 points (95% CI, 6.72-9.82 points) for the placebo group (linear mixed-effects model: $P = .41$). The CDR sum of boxes score increased by 2.87 points (95% CI, 2.44-3.30 points) for the DHA group during 18 months compared with 2.93 points (95% CI, 2.44-3.42 points) for the placebo group (linear mixed-effects model: $P = .68$). In the subpopulation of participants (DHA: 53; placebo: 49), the rate of brain atrophy was not affected by treatment with DHA. Individuals in the DHA group had a mean decline in total brain volume of 24.7 cm^3 (95% CI, 21.4-28.0 cm^3) during 18 months and a 1.32% (95% CI, 1.14%-1.50%) volume decline per year compared with 24.0 cm^3 (95% CI, 20-28 cm^3) for the placebo group during 18 months and a 1.29% (95% CI, 1.07%-1.51%) volume decline per year ($P = .79$).

Conclusion Supplementation with DHA compared with placebo did not slow the rate of cognitive and functional decline in patients with mild to moderate Alzheimer disease.

Quinn et al, JAMA 2010

Valutazione secondo genotipo ApoE

Figure 3. Rate of Cognitive Change on Alzheimer's Disease Assessment Scale (ADAS) Divided by Apolipoprotein E (*APOE*) Genotype



No. of patients								
Placebo	95	89	84	78	66	57	54	48
DHA	137	126	115	106	91	83	69	61

Error bars indicate 95% confidence intervals. The linear mixed-effects analysis finds no effect of docosahexaenoic acid (DHA) on the rate of ADAS-cog change in *APOE* ε4–positive participants but when the analysis is confined to *APOE* ε4-negative participants, the rate of change in ADAS-cog is slower in participants treated with DHA than in participants treated with placebo (linear mixed-effects model: $P=.03$). There was no evidence of a DHA effect on Clinical Dementia Rating sum of boxes, Alzheimer's Disease Cooperative Study activities of daily living, or Neuropsychiatric Inventory on rates of brain atrophy (see "Results" section).

Quinn et al, JAMA 2010

Box 2. Insulin effect in the brain, hyperinsulinemia/diabetes and AD

Insulin exerts diverse functions at the CNS including regulation of neuronal growth and survival, differentiation and migration processes, synaptic remodeling and plasticity. Peripheral insulin enters the CNS by crossing the BBB via a saturable receptor-mediated mechanism. Insulin is also produced in the CNS where it seems to exert a physiological beneficial effect on Aβ clearance [9]. Under conditions of hyperinsulinemia, both insulin transport across the BBB and CNS insulin production are reduced, thus lowering central insulin levels [6]. Interestingly, insulin concentrations in cerebrospinal fluid are low in AD patients and correlate to lower expression of insulin receptors and insulin receptor substrate (IRS); all these changes are proportional to the severity of disease and neurodegeneration, suggesting that an impairment of insulin signaling plays a key role in AD pathogenesis. Furthermore, brain insulin levels inversely correlate with Aβ accumulation and tau phosphorylation [89]. Specifically, insulin affects APP metabolism and trafficking to the plasma membrane and facilitates Aβ release in the extracellular space. Therefore, impaired insulin signaling disrupts APP physiological processing and Aβ metabolism. In the CNS, insulin becomes a substrate for the insulin-degrading enzyme (IDE) and competes with Aβ, thus reducing its clearance [90]. On the other hand, under low-insulin conditions with reduced PI3kinase/AKT signaling and increased GSK3β activation, increased tau phosphorylation results. Lack of stimulation of the WNT pathway that negatively regulates GSK3β under conditions of reduced insulin expression and/or signaling must also be taken into account. Altogether these changes cause abnormalities in PI3K/AKT and WNT signaling that are known to be crucial in AD pathogenesis.

In strong support of a strict correlation between hyperinsulinemia and AD is the observation that raising peripheral insulin levels increases Aβ42 in cerebrospinal fluid, whereas intranasal administration of insulin, that allows distribution exclusively in the CNS, has beneficial effects in AD. These data support a large number of epidemiological studies, either cross-sectional or longitudinal, that show an association between hyperinsulinemia and increased risk of AD [8]. Despite the initial inconsistent and unconvincing results reported for a link between diabetes and risk for AD, a recent re-analysis of several studies with longer follow-up has more clearly demonstrated their association.

Intranasal Insulin Therapy for Alzheimer Disease and Amnestic Mild Cognitive Impairment

Objective: To examine the effects of intranasal insulin administration on cognition, function, cerebral glucose metabolism, and cerebrospinal fluid biomarkers in adults with amnestic mild cognitive impairment or Alzheimer disease (AD).

Design: Randomized, double-blind, placebo-controlled trial.

Setting: Clinical research unit of a Veterans Affairs medical center.

Participants: The intent-to-treat sample consisted of 104 adults with amnestic mild cognitive impairment (n=64) or mild to moderate AD (n=40).

Intervention: Participants received placebo (n=30), 20 IU of insulin (n=36), or 40 IU of insulin (n=38) for 4 months, administered with a nasal drug delivery device (Kurve Technology, Bothell, Washington).

Main Outcome Measures: Primary measures consisted of delayed story recall score and the Dementia Severity Rating Scale score, and secondary measures included the Alzheimer Disease's Assessment Scale–cognitive subscale (ADAS-cog) score and the Alzheimer's Disease Cooperative Study–activities of daily living (ADCS-ADL) scale. A subset of participants underwent lumbar puncture (n=23) and positron emission tomography with fludeoxyglucose F 18 (n=40) before and after treatment.

Results: Outcome measures were analyzed using repeated-measures analysis of covariance. Treatment with 20 IU of insulin improved delayed memory ($P<.05$), and both doses of insulin (20 and 40 IU) preserved caregiver-rated functional ability ($P<.01$). Both insulin doses also preserved general cognition as assessed by the ADAS-cog score for younger participants and functional abilities as assessed by the ADCS-ADL scale for adults with AD ($P<.05$). Cerebrospinal fluid biomarkers did not change for insulin-treated participants as a group, but, in exploratory analyses, changes in memory and function were associated with changes in the Aβ42 level and in the tau protein–to–Aβ42 ratio in cerebrospinal fluid. Placebo-assigned participants showed decreased fludeoxyglucose F 18 uptake in the parietotemporal, frontal, precuneus, and cuneus regions and insulin-minimized progression. No treatment-related severe adverse events occurred.

Conclusions: These results support longer trials of intranasal insulin therapy for patients with amnestic mild cognitive impairment and patients with AD.

Trial Registration: clinicaltrials.gov Identifier: NCT00438568

Arch Neurol. 2012;69(1):29-38. Published online September 12, 2011. doi:10.1001/archneurol.2011.233

Craft et al, 2012

Table 1. Demographics of Intent-to-Treat Sample of 104 Adults With aMCI or Mild to Moderate AD

Demographic	Treatment Group		
	Placebo (n=30)	20 IU of Insulin (n=36)	40 IU of Insulin (n=38)
Age, mean (SEM), y	74.9 (1.6)	72.8 (1.5)	69.9 (1.4)[a]
Education, mean (SEM), y	15.3 (0.6)	15.5 (0.5)	16.2 (0.5)
3MSE score, mean (SEM)	84.2 (2.7)	83.7 (2.5)	84.3 (2.4)
BMI, mean (SEM)	27.4 (0.8)	26.7 (0.8)	26.9 (0.7)
Sex, % of patients			
Male	56.7	61.1	52.6
Female	43.3	38.9	47.4
AChEI treatment, % of patients			
No	60.0	72.2	65.8
Yes	40.0	27.8	34.2
APOE ε4 carriers, % of patients			
No	55.2	50.0	57.9
Yes	44.8	50.0	42.1
Diagnosis, % of patients			
aMCI	70.0	55.6	60.5
AD	30.0	44.4	39.5

Abbreviations: AChEI, acetylcholinesterase inhibitor; AD, Alzheimer disease; aMCI, amnestic mild cognitive impairment; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); 3MSE, modified Mini-Mental State Examination.

[a]The participants who received 40 IU of insulin were younger than the placebo-assigned participants (P=.02).

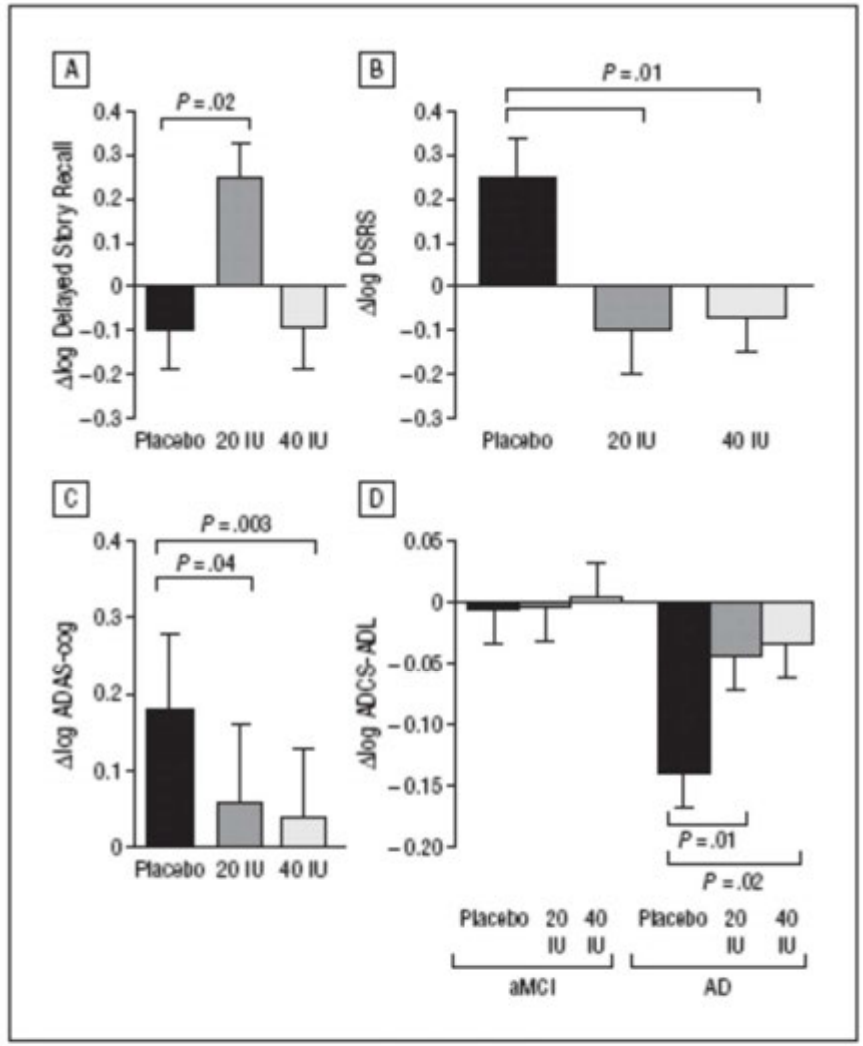


Figure 2. Log mean (A) delayed story recall, (B) Dementia Severity Rating Scale (DSRS), (C) Alzheimer Disease's Assessment Scale–cognitive subscale (ADAS-cog), and (D) Alzheimer's Disease Cooperative Study–activities of daily living (ADCS-ADL) scale change scores (from baseline to month 4) with standard errors of the mean (error bars) for placebo, 20-IU dose insulin, and 40-IU dose insulin groups. All scores are adjusted for age; ADAS-cog scores are further adjusted for the interaction of age with treatment group, and ADCS-ADL scale scores are further adjusted for diagnosis. AD indicates Alzheimer disease; aMCI, amnestic mild cognitive impairment.

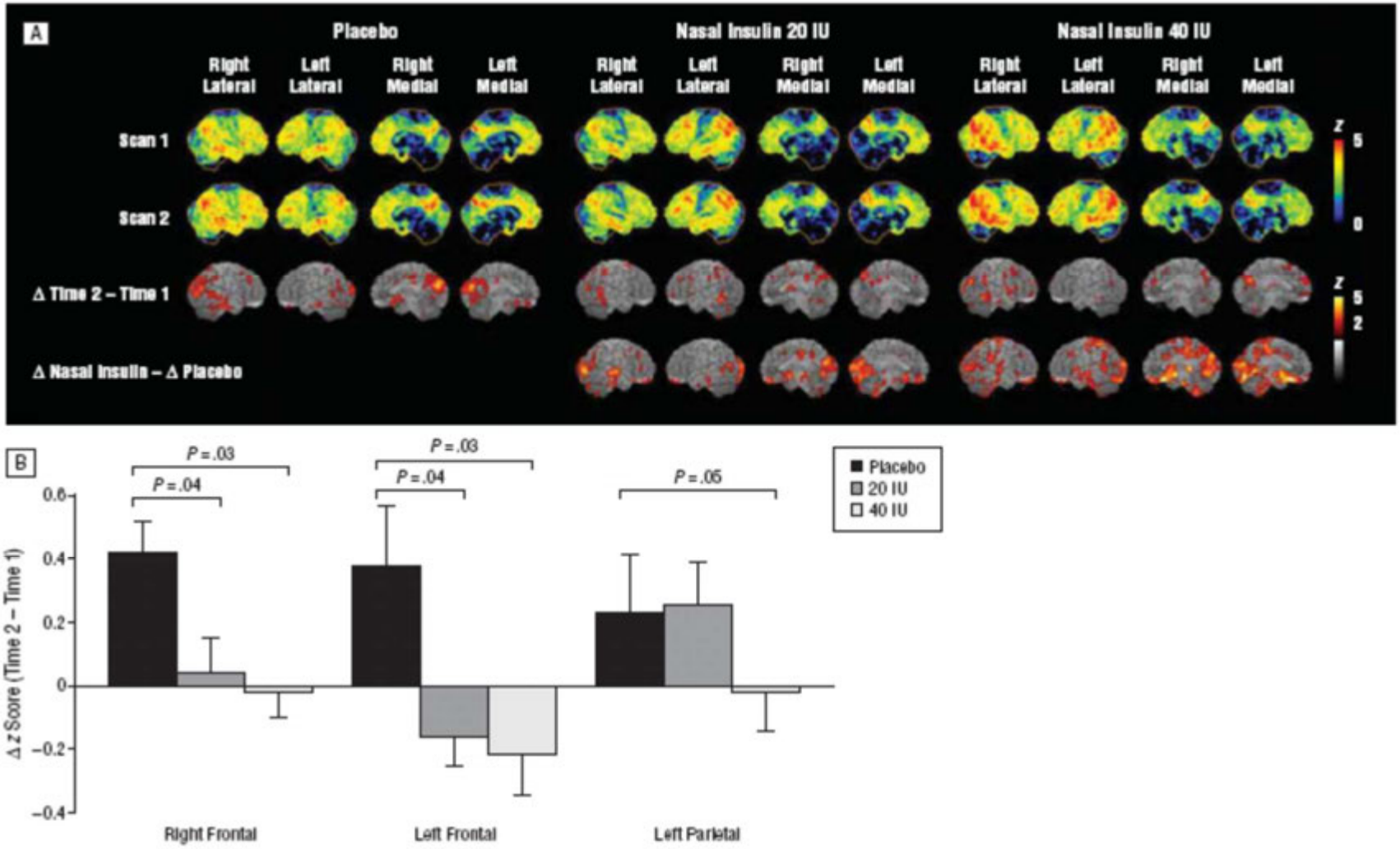


Figure 3. A, Areas of hypometabolism at baseline (scan 1) and month 4 (scan 2), along with changes in hypometabolism (Δ time 2–time 1) within each group, and differences in change between the placebo group and the 20-IU or 40-IU dose insulin group (Δ nasal insulin–Δ placebo). The red and orange colors, compared with the green and blue colors, indicate areas of greater hypometabolism from time 1 to time 2, and from placebo group to insulin groups. B, Change in mean regional *z* scores with standard errors of mean (error bars) for the right and left frontal regions and the left parietal region for the placebo, 20-IU dose insulin, and 40-IU dose insulin groups. For the right and left frontal volume-of-interest (VOI) values, placebo-assigned participants had reduced activity during the 4-month period, whereas the 20-IU and 40-IU dose insulin groups had preserved or slightly increased activity (treatment group × time interaction: $P = .04$ for comparison between placebo group and 20-IU dose insulin group; $P = .03$ for similar comparison between placebo group and 40-IU dose insulin group). Similar analyses for left medial parietal VOI values revealed reduced activity over time for the placebo group compared with the 40-IU dose insulin group (time × treatment group interaction: $P = .05$).

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Advances in the treatment of neurodegenerative disorders employing nanotechnology

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Due to limitations posed by the restrictive blood–brain barrier, conventional drug delivery systems do not provide adequate cyto-architecture restoration and connection patterns that are essential for functional recovery in neurodegenerative disorders (NDs). Nanotechnology employs engineered materials or devices that interact with biological systems at a molecular level and could revolutionize the treatment of NDs by stimulating, responding to, and interacting with target sites to induce physiological responses while minimizing side effects. This review provides a concise discussion of the current applications of nano-enabled drug-delivery systems for the treatment of NDs, in particular Alzheimer's and Parkinson's diseases, and explores the future applications of nanotechnology in clinical neuroscience to develop innovative therapeutic modalities for the treatment of NDs.

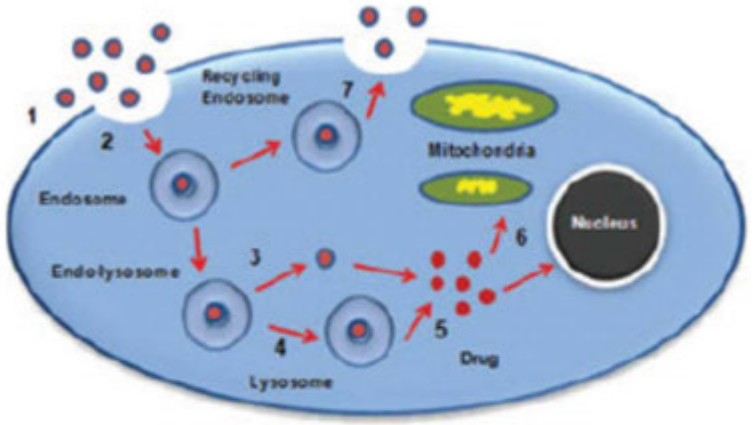

Figure 1. Steps detailing the cytosolic delivery of neurotherapeutic agents via nanoparticles (NPs), 1) cellular association of NPs, 2) internalization of NPs via endocytosis, 3) endosomal escape of NPs or 4) lysosomal degradation of NPs, 5) drug freely diffusing into cytoplasm, 6) cytoplasmic transport of drug to target organelle, 7) exocytosis of NPs.

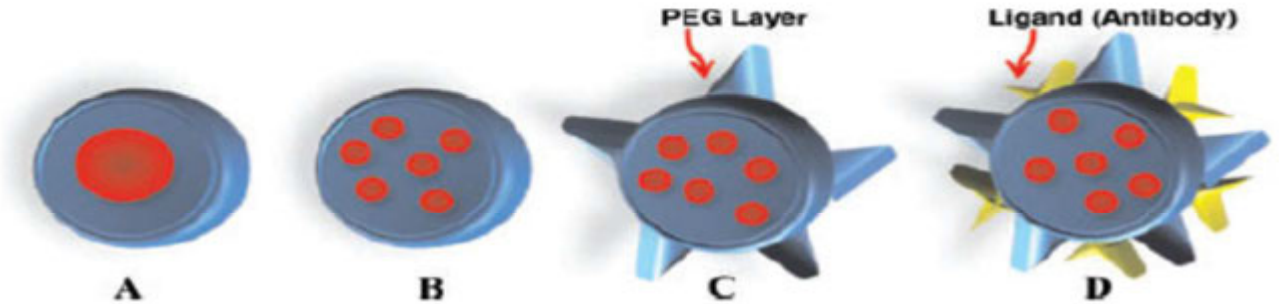

Figure 2. Types of nanoparticles for transport of drugs into the CNS, (A) nanocapsules, (B–D) nanospheres with drug distributed throughout a polymer/lipid matrix, (B) either without a surface coating or coating with a surfactant and/or PEG layer, and (D) additional coating with antibodies and/or ligands.

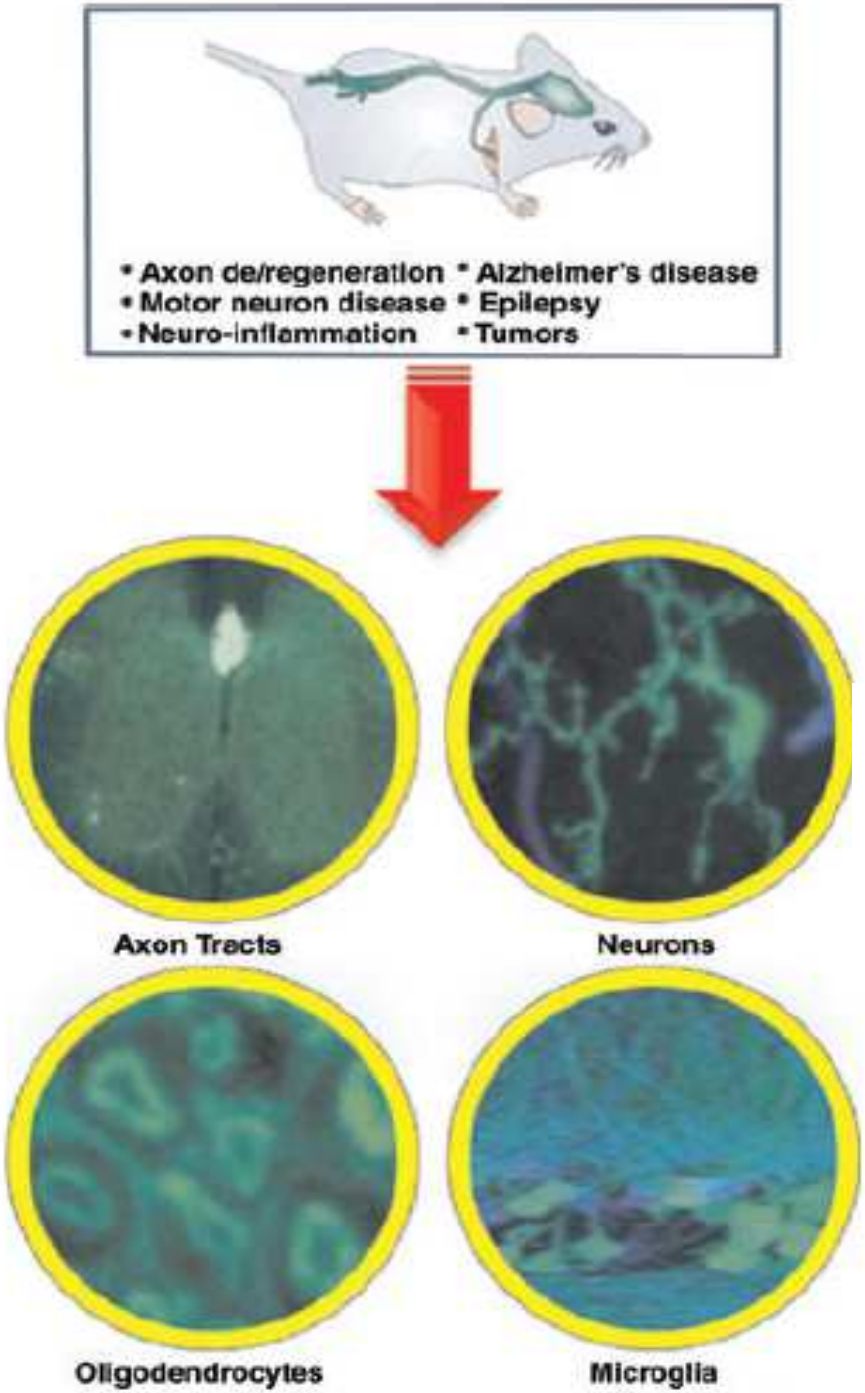

Figure 9. *In vivo* imaging of encapsulated *ThT* poly(butylcyanoacrylate) nanocapsules delivered to the mouse brain by direct intrahippocampal injection.

FGF2 gene transfer restores hippocampal functions in mouse models of Alzheimer's disease and has therapeutic implications for neurocognitive disorders

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MOLECULAR NEURODEGENERATION

REVIEW Open Access

Adult hippocampal neurogenesis and its role in Alzheimer's disease

Yangling Mu* and Fred H Gage

Abstract

The hippocampus, a brain area critical for learning and memory, is especially vulnerable to damage at early stages of Alzheimer's disease (AD). Emerging evidence has indicated that altered neurogenesis in the adult hippocampus represents an early critical event in the course of AD. Although causal links have not been established, a variety of key molecules involved in AD pathogenesis have been shown to impact new neuron generation, either positively or negatively. From a functional point of view, hippocampal neurogenesis plays an important role in structural plasticity and network maintenance. Therefore, dysfunctional neurogenesis resulting from early subtle disease manifestations may in turn exacerbate neuronal vulnerability to AD and contribute to memory impairment, whereas enhanced neurogenesis may be a compensatory response and represent an endogenous brain repair mechanism. Here we review recent findings on alterations of neurogenesis associated with pathogenesis of AD, and we discuss the potential of neurogenesis-based diagnostics and therapeutic strategies for AD.

Keywords: Alzheimer's disease, adult neurogenesis, hippocampus, neural stem cell

Farmaci e anziani

Grazie a tutti/e … per l'attenzione

(e la pazienza…….)