GRANADA; 28 Enero 2011

Diabetes y demencia

Dr. Francesc Formiga. Servicio de Medicina Interna. Unidad de Geriatría
Hospital Universitario de Bellvitge. L'Hospitalet de Llobregat, Barcelona

Geriatr Gerontol Int 2009; 9: 105–114

REVIEW ARTICLE

Diabetes mellitus and geriatric syndromes

Atsushi Araki and Hideki Ito

Table 2 Assessment of typical geriatric syndromes in diabetes mellitus

Geriatric syndrome	Tools and risk assessment
Disability	Basic activities of daily living (ADL), instrumental ADL
Depression or low quality of life	15-Item Geriatric Depression Scale (GDS-15, GDS-5), PGC morale scale
Fall	Frequency of fall, gait, balance, blood pressures (supine and standing)
Urinary incontinence	Frequency and severity of incontinence, postvoid residual urine volume, nocturia
Dementia	Mini-Mental State Examination (MMSE)
Malnutrition	Subjective global assessment (SGA), Mini-Nutritional Assessment (MNA), objective data assessment (e.g. serum albumin, BMI, lymphocyte number)
Visual disturbance	Visual acuity

Clasificación etiológica de las demencias

- Enfermedades cerebrales primarias
- Enfermedad de Alzheimer
- Enfermedad de Pick
- Enfermedad por cuerpos de Lewy
- Enfermedad de Parkinson
- Corea de Huntington
- Demencia vascular
- Demencia postraum
- Hematoma subdura
- Demencia pugilística
- Neoplasias intracran
- Hidrocefalia normote
- Enfermedades infecci
- Demencia postencefal
- Enfermedad de Creutz -Jakob
- SIDA, Neurolúes

Demencia tipo Alzheimer:
50 a 65%
Demencia vascular :
15 a 20%
Demencias Mixtas :
14%

- Encefaloparía hepática, Encf urémica
- Hiper e hiponatremia
- Hipoxia
- Defi de vitamina Bl2-folato
- calcemia
- a
- roidea
- rticoadrenal
- autoinmunes (LES, vasculitis
- tiamina (vit. B 1)
- tia alcohólica (toxicocarencial)
- a
- Dependencia a sustancias
- Intoxicación por metales pesados
- Alcoholismo crónico

¿Es la DM un factor de riesgo para EA?

1. **¿Que nos dicen los estudios epidemiológicos?**

¿Que dicen los estudios epidemiológicos?

- **En los últimos años, existe amplia evidencia epidemiológica en estudios LONGUITUDINALES que relaciona los factores de riesgo cardiovascular con el deterioro cognitivo y la EA.**

- **Estos estudios cuentan con un elevado número de participantes, representan culturas diversas y llegan a conclusiones similares en poblaciones muy distintas.**

Duron E, Hanon O. Vascular risk factors, cognitive decline, and dementia. Vas Health Risk Manag. 2008;4:363-381.

De la Torre JC. Alzheimer disease as a vascular disorder: nosological evidence. Stroke. 2002;33:1152-1162.

Hofman A, Breteler MMB, Van Duijn CM, Krestin GP, Pols HA, Stricker BHC. The Rotterdam Study: objectives and design update. Eur J Epidemiol. 2007;22:819-829.

The relationship between type 2 diabetes and cognitive dysfunction: longitudinal studies and their methodological limitations

Kate V. Allen[a], Brian M. Frier[a], Mark W.J. Strachan[b,*]

European Journal of Pharmacology 490 (2004) 169–175

Abstract

Type 2 diabetes and dementia in the elderly are major public health pro… …s-sectional studies have suggested that these two conditions may be inter-related, but the nature of this ass… …n can only be established through studies with a longitudinal design, taking into account the many… …ny study of cognition. A literature search has identified 10 studies (nine population-based an… …included a definable diabetic population and assessments of cognitive function at bas… …d a combination of domain-specific cognitive assessments and a clinical diag… …on. Diabetes was associated with either an accelerated cognitive decline o… …f the population-based studies. One study demonstrated a relationship betw… …th other types of dementia. No association between type 2 diabetes and cogn… …y. These studies provide compelling evidence to support the view that people w… …eloping cognitive impairment in comparison with the general population.

9 de los 10 estudios SI

DM se asocia a empeoramiento de la cognición

¿Que dicen los estudios epidemiológicos?

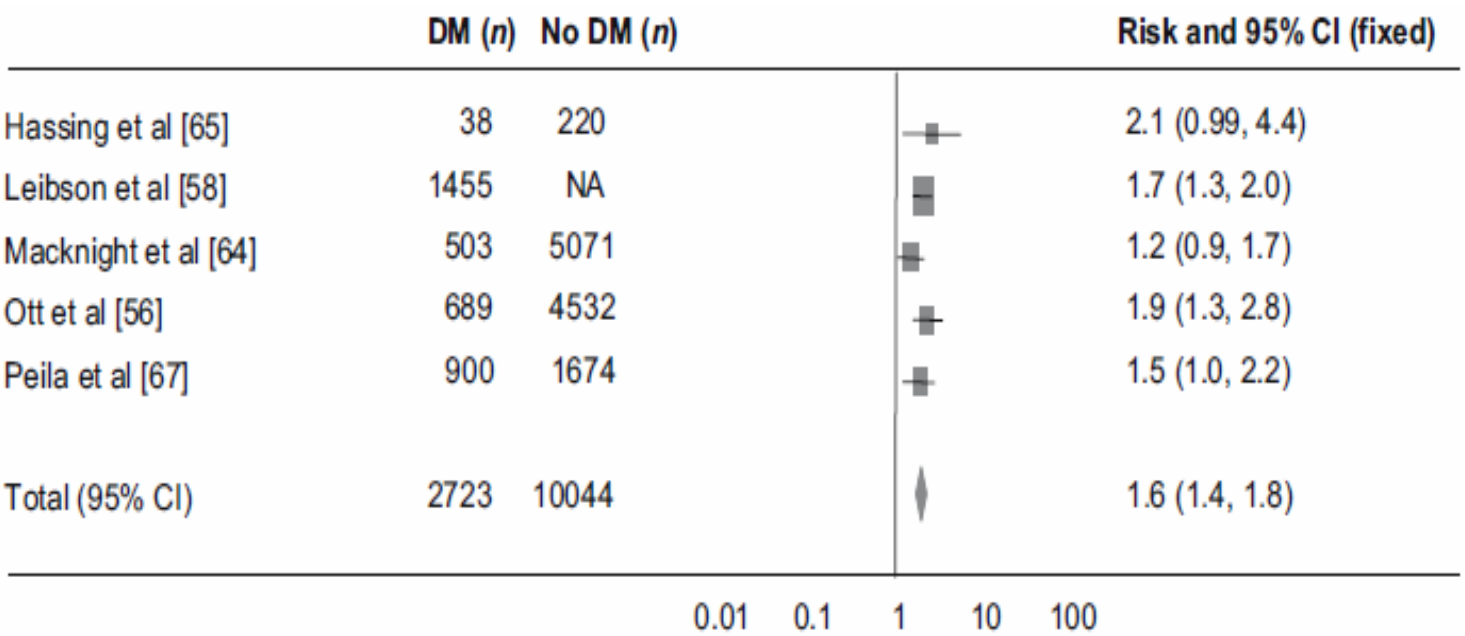


Fig. 3 Development of future dementia. Figure shows the risk of future dementia in diabetic (DM) versus non-diabetic (No DM) patients, as well as the pooled estimate. Test for heterogeneity: chi square=4.02, *df*=4 (p=0.40), I^2=0.6%

Diabetologia (2005) 48: 2460–2469

¿Que dicen los estudios epidemiológicos?

Table 1a
Risk of dementia associated with type 2 diabetes mellitus

	FU (y)	N baseline/FU	Diabetes baseline	Age		Any dementia		Alzheimer's disease	
						[illegible]s[a] (CI)	Additionally adjusted results[b]	Results (95% CI)	Additionally adjusted results
Whitmer et al., 2005b	~35	ND/8845				[illegible]–1.8)	–	–	–
Yamada et al., 2003	30	ND/1774					–	4.4 ($p<0.01$)	–
Schnaider-Beeri et al., 2004	35	100[illegible]					2.8 (1.4–5.7)	–	–
Curb et al., 1999	25					[illegible].8)	–	1.0 (0.5–2.0)	–
Ott et al., 1999						[illegible].8)	–	1.9 (1.2–3.1)	–
Akomolafe et al., 2006	1[illegible]					[illegible].8)	1.2 (0.7–2.0)	1.1 (0.7–1.8)	1.2 (0.7–2.1)
Yoshitake et al., 1995	7						–	2.2 (1.0–4.9)	–
MacKnight et al., 2002	5					[illegible].2 (0.9–1.7)	1.3 (0.9–1.8)	1.2 (0.8–1.8)	1.3 (0.8–2.0)
Arvanitakis et al., 2004	5.5				[illegible]	–	–	1.7 (1.1–2.5)	–
Luchsinger et al., 2001	4.3				6	–	–	–	–
Luchsinger et al., 2005	5.5			76	6	–	–	2.4 (1.8–3.2)	2.0 (1.4–2.9)
Peila et al., 2002	2.9		[illegible]900	77	7	1.5 (1.0–2.2)	1.5 (1.0–2.2)	1.7 (1.0–2.8)	1.8 (1.1–2.9)
Xu et al., 2004	4.7	130[c]	114/ND	81	7	1.5 (1.1–2.1)	1.5 (1.0–2.1)	1.3 (0.8–1.9)	1.3 (0.9–2.1)
Hassing et al., 2002	6	702[d]	ND/108	83	4	–	1.2 (0.8–1.7)	–	0.8 (0.5–1.5)

Estudio Monjas: 2005
65% incremento

Estudio Rotterdam: 2000
Doble riesgo

European Journal of Pharmacology 585 (2008) 97–108

Type 2 Diabetes and Cognitive Decline in Middle-Aged Men and Women

The Doetinchem Cohort Study

OBJECTIVE — To test the hypothesis that type 2 diabetes is associated with greater decline in cognitive function in middle-aged individuals.

RESEARCH DESIGN AND METHODS — In the Dutch prospective Doetinchem Cohort Study, cognitive functioning was measured twice within a 5-year time interval in 2,613 men and women. Participants were aged 43–70 years at baseline (1995–2002), and no one had a history of stroke. Change in scores on global cognitive function as well as on specific cognitive function domains (memory, speed of cognitive processes, and cognitive flexibility) were compared for respondents with and without type 2 diabetes (verified by the general practitioner or random plasma glucose levels ≥11.1 mmol/l).

RESULTS — At the 5-year follow-up, the decline in global cognitive function in diabetic patients was 2.6 times greater than that in individuals without diabetes. For individuals aged ≥60 years, patients with incident and prevalent diabetes showed a 2.5 and 3.6 times greater decline, respectively, in cognitive flexibility than individuals without diabetes. For most cognitive domains, the magnitude of cognitive decline in patients with incident diabetes was intermediate between that of individuals without diabetes and that of patients with diabetes at baseline.

CONCLUSIONS — Middle-aged individuals with type 2 diabetes showed a greater decline in cognitive function than middle-aged individuals without diabetes.

Diabetes Care 33:1964–1969, 2010

Diabetes Mellitus and Risk of Developing Alzheimer Disease

Results From the Framingham Study

Abimbola Akomolafe, MD, MPH, MS; Alexa Beiser, PhD; James B. Meigs, MD, MPH; Rhoda Au, PhD

Results: At baseline, 202 participants (9.1%) had DM. During the follow-up period (mean, 12.7 years; range, 1-20 years), 17 of 202 persons with DM (8.4%) and 220 of 2008 persons without DM (11.0%) developed AD, yielding a relative risk of 1.15 (95% confidence interval, 0.65-2.05). Among subjects without an apolipoprotein E ε4 allele or elevated plasma homocysteine levels, 44 of 684 persons (6.4%) developed AD; relative risk for AD comparing diabetic patients with nondiabetic patients was 2.98 (95% confidence interval, 1.06-8.39; $P=.03$). The effect was strongest in persons aged 75 years or older with a relative risk of 4.77 (95% confidence interval, 1.28-17.72; $P=.02$).

Conclusion: Diabetes mellitus did not increase the risk of incident AD in the Framingham cohort overall; however, DM may be a risk factor for AD in the absence of other known major AD risk factors.

Arch Neurol. 2006;63:1551-1555

Enhanced Risk for Alzheimer Disease in Persons With Type 2 Diabetes and *APOE* ε4

The Cardiovascular Health Study Cognition Study

Fumiko Irie, MD, PhD, MPH; Annette L. Fitzpatrick, PhD; Oscar L. Lopez, MD; Lewis H. Kuller, MD, DrPH;

Results: Compared with those who had neither type 2 diabetes nor *APOE* ε4, those with both factors had a significantly higher risk of AD (hazard ratio, 4.58; 95% confidence interval, 2.18-9.65) and mixed AD (hazard ratio, 3.89; 95% confidence interval, 1.46-10.40).

Conclusion: These data suggest that having both diabetes and *APOE* ε4 increases the risk of dementia, especially for AD and mixed AD.

Arch Neurol. 2008;65(1):89-93

A Summary Risk Score for the Prediction of Alzheimer Disease in Elderly Persons

Reitz, C. et al. Arch Neurol 2010;67:835-841.

Table 4. Cox Proportional Hazards Models Relating the Risk Factors Profiles With Risk of LOAD

	Probable and Possible LOAD (n=92)				Probable LOAD (n=80)			
Characteristic	β	*P* Value	HR (95% CI)	Risk Score	β	*P* Value	HR (95% CI)	Risk Score
Sex								
M	0		1 [Reference]	0	0		1 [Reference]	0
F	0.14	.66	1.15 (0.61-2.21)	1	0.13	.7	1.14 (0.51-2.54)	1
Age, y								
65-70	0		1 [Reference]	0	0		1 [Reference]	0
>70-75	0.809	.14	2.246 (0.76-6.62)	6	0.776	.22	2.174 (0.623-7.587)	6
>75-80	1.12	.04	3.065 (1.03-9.09)	8	1.559	.01	4.754 (1.447-15.614)	12
>80-85	1.862	.001	6.433 (2.07- 20.03)	13	1.861	.006	6.433 (1.710-24.204)	14
>85	2.892	<.001	18.023 (5.93-54.77)	21	3.295	<.001	26.991 (7.797-93.434)	25
Diabetes								
No	0		1 [Reference]	0	0		1 [Reference]	0
Yes	0.461	.16	1.586 (0.83 to 3.01)	3	0.216	.58	1.241 (0.577-2.671)	2
Hypertension								
No	0		1 [Reference]	0	0		1 [Reference]	0
Yes	0.147	.63	1.158 (0.64-2.11)	1	0.027	.93	1.027 (0.540-1.953)	0
Current smoking								
No	0		1 [Reference]	0	0		1 [Reference]	0
Yes	0.684	.10	1.981 (0.88-4.49)	5	0.925	.04	2.521 (1.027-6.191)	7
Low HDL-C								
No	0		1 [Reference]	0	0		1 [Reference]	0
Yes	0.47	.21	1.6 (0.77-3.32)	3	0.466	.26	1.58 (0.711-3.541)	4
High WHR								
No	0		1 [Reference]	0	0		1 [Reference]	0
Yes	0.967	.003	2.629 (1.39-4.97)	7	1.139	.002	3.124 (1.542-6.327)	9
Education, y								
>9	0		1 [Reference]	0	0		1 [Reference]	0
7-9	1.103	.009	3.014 (1.32-6.87)	8	1.074	.02	2.928 (1.187-7.226)	8
0-6	1.506	0	4.507 (2.09-9.74)	11	1.325	.002	3.761 (1.612-8.773)	10
Ethnicity								
White	0		1 [Reference]	0	0		1 [Reference]	0
Black	0.664	.12	1.942 (0.84-4.52)	5	0.598	.23	1.819 (0.686-4.822)	5
Hispanic	0.522	.27	1.685 (0.67-4.22)	4	0.897	.08	2.451 (0.895-6.715)	7
APOE ε4 allele								
None	0		1 [Reference]	0	0		1 [Reference]	0
≥1	0.604	.04	1.829 (1.02-3.29)	4	0.616	.07	1.851 (0.961-3.566)	5

Abbreviations: CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LOAD, late-onset Alzheimer disease; WHR, waist to hip ratio.

Cox Proportional Hazards Models Relating the Risk Factors Profiles With Risk of Late Onset Alzheimer Disease

ARCHIVES OF NEUROLOGY

Diabetologia (2006) 49:2015–2023
DOI 10.1007/s00125-006-0333-1

ARTICLE

La asociación es menor en los mayores de 85 años

T ellitus on cognitive decline i prospective population-based study

· G. J. Biessels ·
stendorp

Received: 19 January 2006 / Accepted: 5 May 2006 / Published online: 28 June 2006

Abstract
Aims/hypothesis Diabetes mellitus is a risk factor for the development of cognitive impairment and dementia in the general population up to 75 years of age. As part of the Leiden 85-plus Study we studied the effects of diabetes on cognition in the oldest old.
Subjects and methods The Leiden 85-plus Study is a prospective population-based study of 599 persons from age 85 onward. Cognitive function was assessed each year from ages 85 to 90 by means of four neuropsychological tests. The presence of diabetes and vascular disease was recorded at baseline, HbA_{1c} was assessed by means of a blood sample at ages 85 and 90. The cross-sectional and prospective associations between diabetes and cognitive function were analysed with linear mixed models, adjusted for sex and level of education.
Results At age 85, diabetes was associated with a lower level of cognitive functioning on the Letter Digit Coding test and the Stroop Test. Diabetes was not associated with accelerated cognitive decline during follow-up. Within the group of diabetic patients, macrovascular disease was the most important determinant of cognitive dysfunction.
Conclusions/interpretation The association between diabetes and accelerated cognitive decline, which has been documented previously in patients up to 75 years of age, may be less evident after age 85. This suggests that the damage occurs in previous years and that therapies aimed at preventing cognitive decline and dementia should focus on the younger old.

Keywords Diabetes mellitus · Cognitive decline · Oldest old

Abbreviations
MMSE Mini-Mental State Examination
GDS-15 15-item Geriatric Depression Scale

Insulin metabolism and the risk of Alzheimer disease

The Rotterdam Study

Results: During follow-up, 211 participants developed AD, 71 of them within 3 years of baseline. Levels of insulin and insulin resistance were associated with a higher risk of AD within 3 years of baseline. After 3 years, the risk was no longer increased. Glucose was not associated with a higher risk of AD. There was no interaction of *APOE* ϵ4 carriership and insulin metabolism on the risk of AD.

Conclusions: Our findings suggest that insulin metabolism influences the clinical manifestation of AD only within 3 years. *Neurology*® 2010;75:1982-1987

Es la DM un factor de riesgo para EA

1. **¿Que nos dicen los estudios epidemiológicos?**

SI

Pero……

¿Que dicen los estudios epidemiológicos?

- **DIFERENCIAS METODOLOGICAS.**
  Dudas debido al tamaño diferente de los estudios.

  Dudas sobre la comparabilidad de los grupos: la mayoría aparean por edad, genero, educación pero por ejemplo no por cardiopatía isquémica.
- **DIFERENTES DEFINICIONES DM.**

  Posible sesgo por aparición no comprobada de nueva diabetes durante el seguimiento en el grupo control.
- **DUDAS SOBRE LA ELECCION DE LOS TEST**
  (muy diversos) y posible fenómeno de aprendizaje por su repetición. En general test diagnósticos poco útiles para EA inicial.

¿Que nos dicen los estudios epidemiológicos?

- **No inclusión en los estudios de pacientes institucionalizados.**
- **Posible sesgo supervivencia.**
- **Poco análisis de la comorbilidad (depresión, etc), del tratamiento farmacológico y de la predisposición genética.**

- **ESTUDIOS EN MARCHA:**

  Como el The Edinburgh Type 2 Diabetes Study (ET2DS).

¿Que dicen los estudios epidemiológicos?

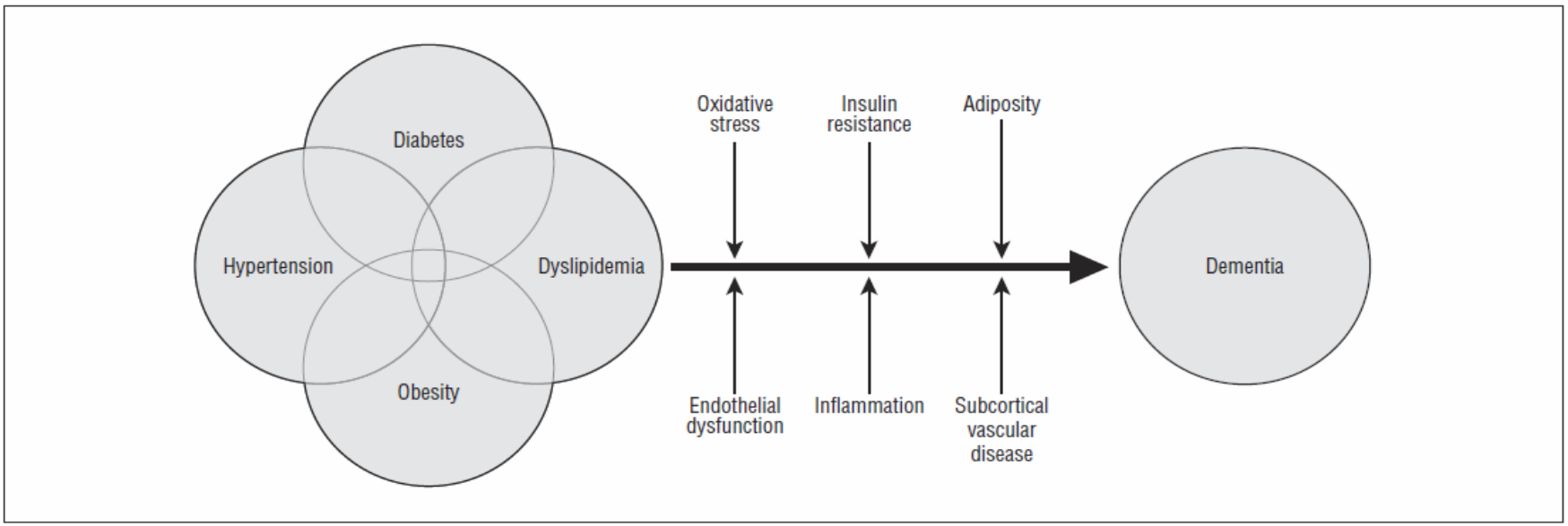


Figure. Possible mechanisms that may explain the association between vascular risk factors and an increased risk of developing dementia.

¿Que dicen los estudios epidemiológicos?

Table 2
Risk of dementia attributable to vascular risk factors

	Midlife (45–65 years) risk factor assessment		
	Odds ratio for dementia[a]	Estimated prevalence[b] (%)	Estimated population attributable risk (%)
Diabetes	2.2 (4)	2–8	2–9
Hypertension	2.3 (3)	30–40	28–36
Dyslipidaemia	2.1 (3)	20–25	18–22
Obesity	2.0 (3)	35–40	26–29

R.P. Kloppenborg et al. / European Journal of Pharmacology 585 (2008) 97–108

¿Que dicen los estudios epidemiológicos?

Table 2
Risk of dementia attributable to vascular risk factors

	Late life (>65 years) risk factor assessment		
	Odds ratio for dementia	Estimated prevalence (%)	Estimated population attributable risk
Diabetes	1.6 (10)	10–15	6–8%
Hypertension	1.1 (7)	55–80	5–7%
Dyslipidaemia	1.0 (4)	10–20	≤0
Obesity	0.8 (2)	25–30	≤0

R.P. Kloppenborg et al. / European Journal of Pharmacology 585 (2008) 97–108

¿Es la DM un factor de riesgo para EA?

2. ¿Existe una explicación fisiopatológica?

O bien es una asociación casual

Interacción entre DM y EA: Varios mecanismos además del vascular

1. **En el cerebro, la hiperinsulinemia inicial y la resistencia a la insulina pueden provocar apoptosis neuronal y la formación de placas neuríticas y ovillos neurofibrilares : ¿Diabetes tipo 3?**

2. **Modulando las concentraciones de acetilcolina especialmente en el hipocampo.**

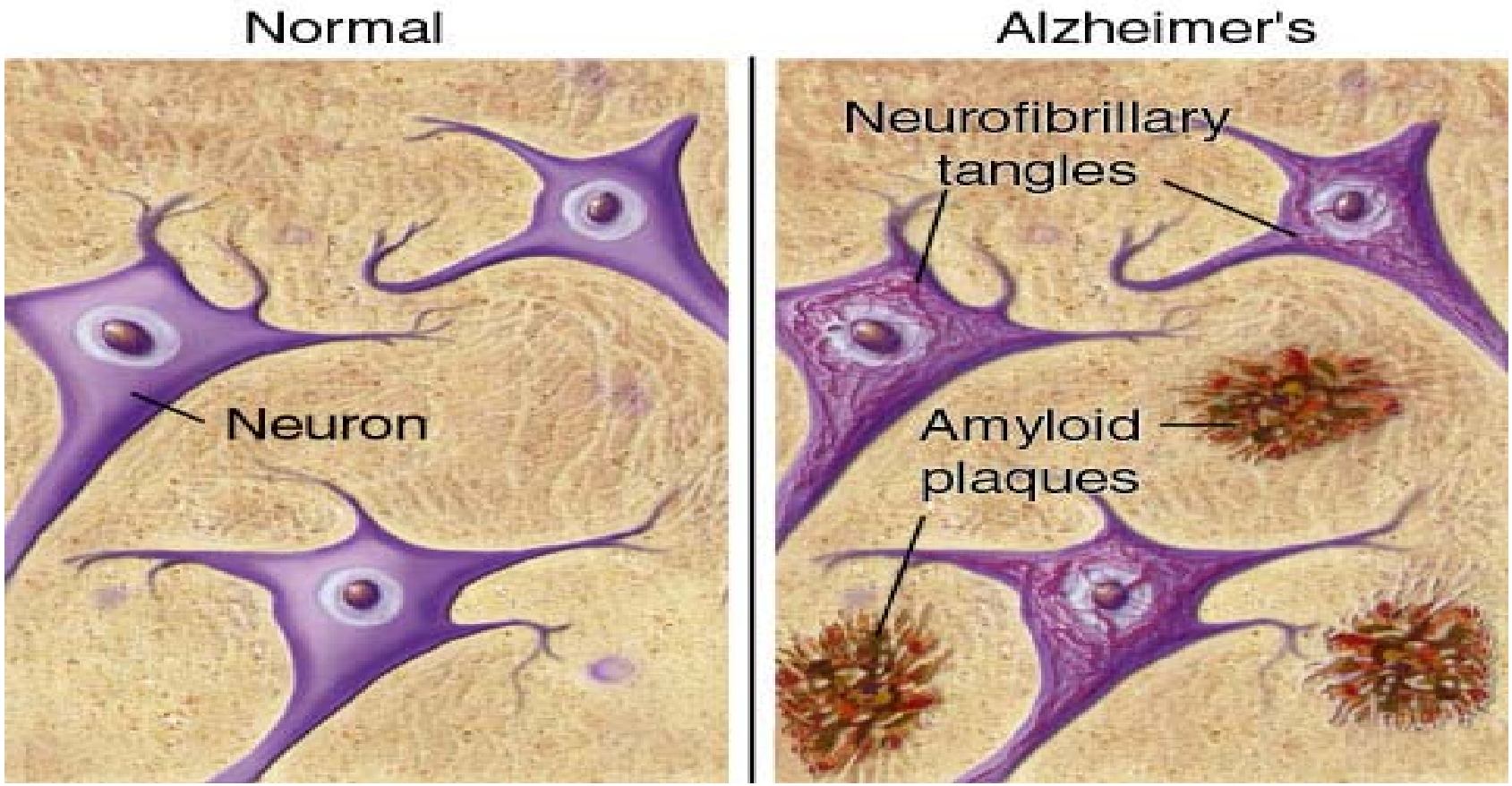
3. **Acción de los productos finales de glucosilación avanzada (AGEs)**

4. **La proteína relacionada con el receptor de lipoproteína (LRP-1).**

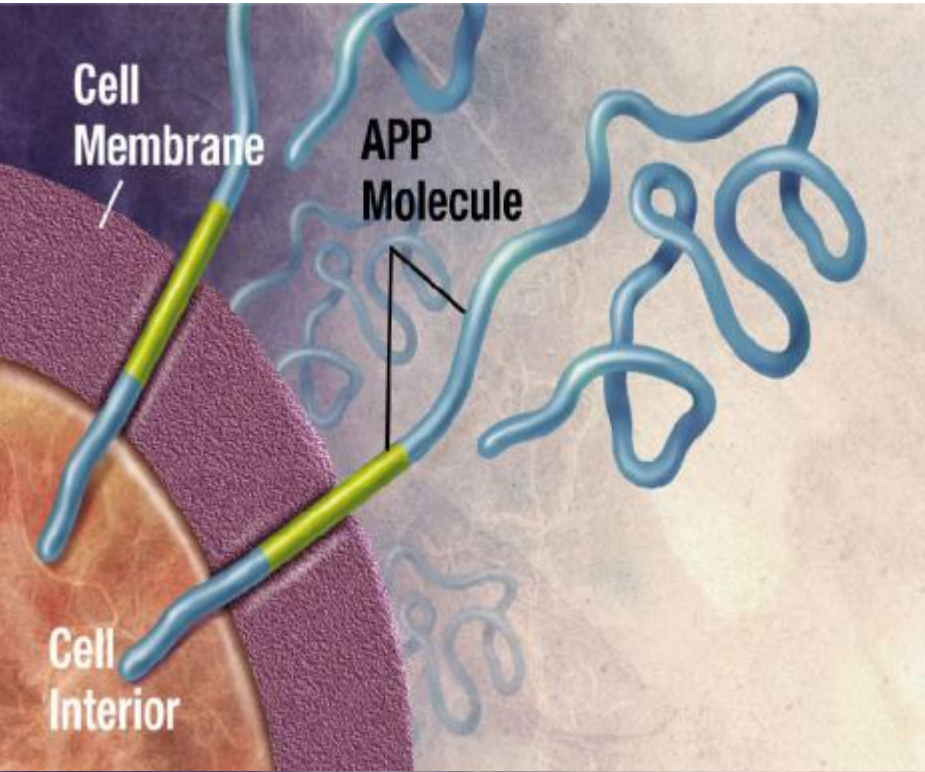
Common features between diabetes mellitus and Alzheimer's disease

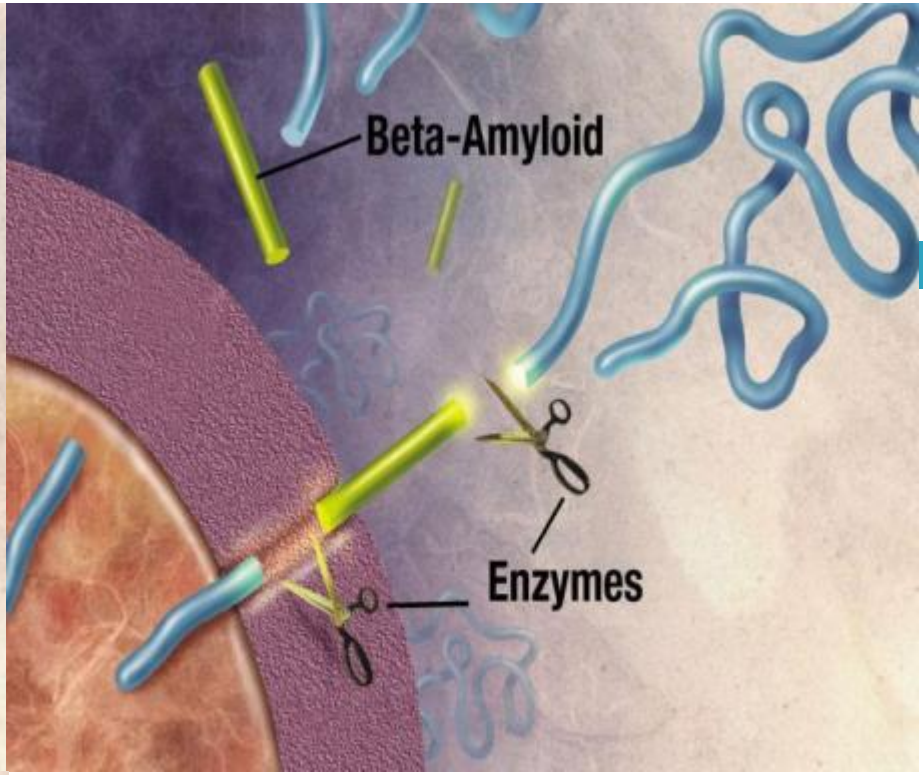
J. Götz*, L. M. Ittner and Y.-A. Lim

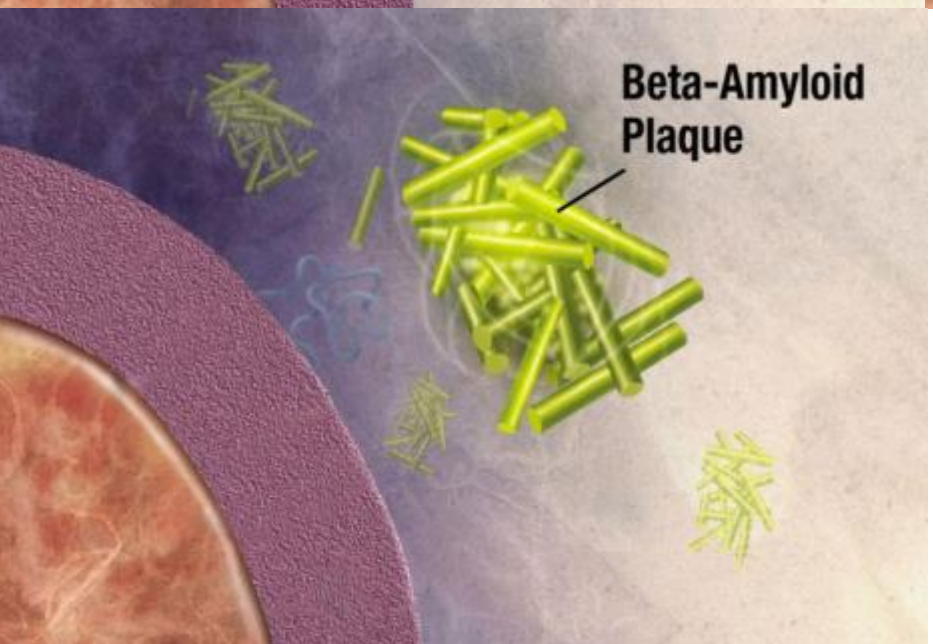
Cell. Mol. Life Sci. 66 (2009) 1321 – 1325



Deterioro función sináptica por deposito péptido beta-amiloide debido a la degradacion de la PPA (proteina precursora amiloide)

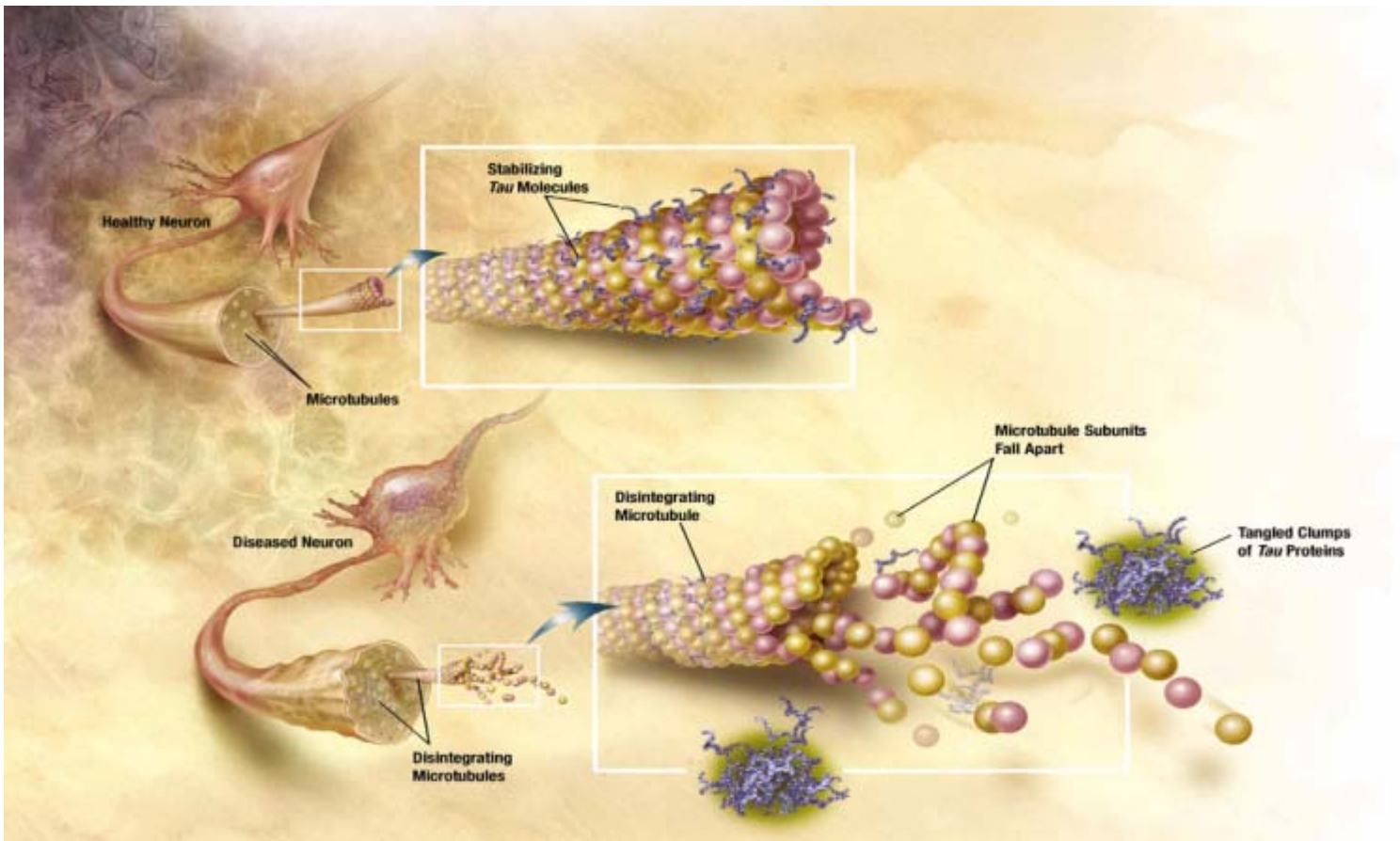






Formación de placas neuriticas.

Formación ovillos Neurofibrilares



Neuropatología

- **En cuanto a los depósitos intracelulares, constituyen la degeneración neurofibrilar, cuyo principal componente es la proteína tau.**
  La proteína tau normal forma los "puentes" que mantienen correctamente unidos los microtúbulos que conforman el citoesqueleto neuronal.

- **En la EA (en parte por la acción tóxica del β-amiloide) se produce una hiperfosforilación anómala, alterándose el citoesqueleto y dando lugar a la degeneración neurofibrilar, con la formación de los ovillos neurofibrilares.**

Neuropatología

- **Exceso de beta-amiloide puede ser eliminado a través de la proteína relacionada con el receptor de lipoproteína o bien por un proceso de degradacion en que interviene la enzima degradante de Insulina (EDI)**.

Interacción entre DM y EA: ¿Por qué la insulina se asocia a mejor cognición?

- **La insulina atraviesa la BHE.**
- **En condiciones normales los niveles de insulina cerebral se correlacionan con las concentraciones periféricas. La hiperinsulinemia periférica crónica comporta una disminución del transporte de insulina a través de la BHE.**
- **En el cerebro la insulina modula conjuntamente con la leptina el ciclo apetito-saciedad y favorece el aprendizaje y la memoria a largo plazo.**

Interacción entre DM y EA: ¿Por qué la insulina se asocia a mejor cognición?

Los receptores de Insulina están ampliamente distribuidos a través del cerebro (más en el hipocampo, hipotálamo, bulbo olfatorio y cerebelo) y particularmente concentrados en las terminaciones sinápticas.

La insulina al unirse a un receptor en la sinapsis, inicia el mecanismo necesario para que las cels. nerviosas sobrevivan y se formen los recuerdos.

La insulino-resistencia obligara a mayores cantidades de Insulina para facilitar la memoria.

¿Existe una diabetes tipo 3?

La hiperinsulinemia en respuesta a la resistencia a la Insulina comporta disminución Insulina cerebral y una mala regulación EDI, así se acumula β-amiloide por descenso de su degradación por la EDI.

Hay un descenso de Insulina en el CEREBRO y una resistencia a los receptores de Insulina:
Los pacientes con EA pueden tener concentraciones de glucosa en LCR menores que las personas sanas: ¿diabetes tipo 3?.

Steen E, et al. Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease--is this type 3 diabetes? J Alzheimers Dis. 2005; 7 :3-80.

¿Existe una diabetes tipo 3?

La hiperinsulinemia en respuesta a la resistencia a la Insulina comporta disminución Insulina cerebral y una mala regulación EDI, así se acumula β-amiloide por descenso de su degradación por la EDI. ¿diabetes tipo 3?.

DM2: niveles altos insulina e insulin resistencia que comportan una reducción en la insulina del cerebro.

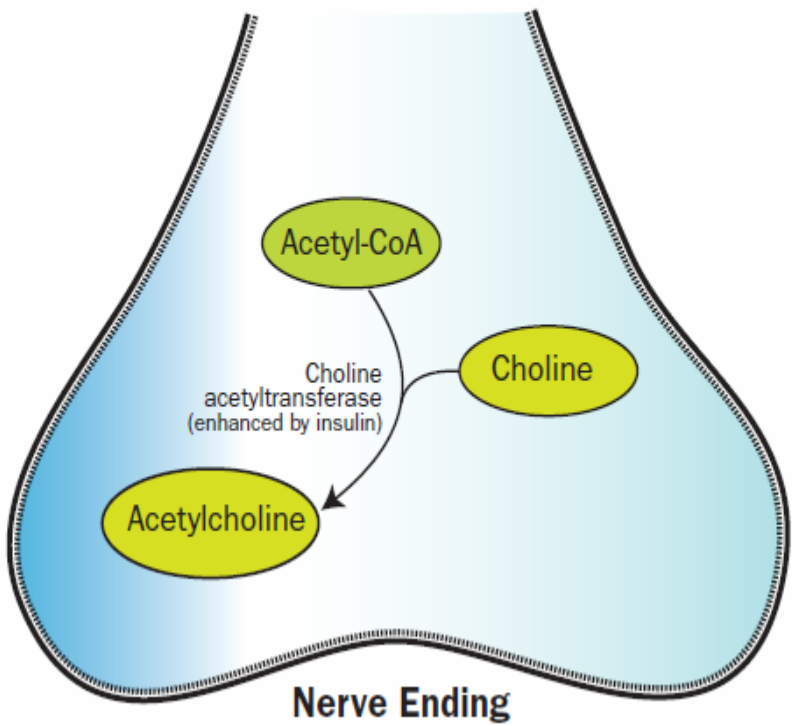
EA: niveles bajos insulina e insulinresistencia en SNC.

Steen E, et al. Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease--is this type 3 diabetes? J Alzheimers Dis. 2005; 7 :3-80.

Hipótesis colinérgica

(*Altern Med Rev* 2009;14(4):373-379)

Figure 2. Insulin's Role in the Cholinergic Hypothesis: The Importance of Insulin in Memory Formation



La Insulina estimula la expresión de la acetilcolintransferasa responsable de la síntesis de acetilcolina.

Rivera EJ. Insulin and insulin-like growth factor expression and function deteriorate with progression of Alzheimer's disease: link to brain reductions in acetylcholine. J Alzheimers Dis. 2005; 8:247-68.

Los productos finales de glucosilación avanzada (AGEs)

- **Los productos finales de la glucosilación avanzada (AGEs) se forman en una amplia variedad de proteínas.**

  IMPORTANTE mecanismo para el desarrollo de las complicaciones de la DM.

- **Las personas con DM pueden tener mayor riesgo de EA debido a la producción de AGEs, y al aumento en la expresión del receptor (RAGEs) que pueden producir daño neuronal.**

Takeuchi M. Possible involvement of advanced glycation end-products (AGEs) in the pathogenesis of Alzheimer's disease. Curr Pharm Des 2008; 14:973-8.

Proteína relacionada con el receptor de lipoproteína-1

- La proteína relacionada con el receptor de lipoproteína (LRP-1), ayuda a elimina β-amiloide del plasma y también facilita el transporte del mismo fuera del cerebro.

- LRP-1 disminuye cuando existe insulin-resistencia lo que induce a la acumulación de β-amiloide.

Sagare A, et al. Clearance of amyloid-beta by circulating lipoprotein receptors. Nat Med. 2007; 13: 1029–31

Clearance of amyloid-β peptide across the blood-brain barrier: Implication for therapies in Alzheimer's disease

R Deane, RD Bell, A Sagare, and BV Zlokovic

IMPLICACIONES TERAPEUTICAS iiiiiiiii

The main receptors for amyloid-beta peptide (Aβ) transport across the blood-brain barrier (BBB) from brain to blood and blood to brain are low-density lipoprotein receptor related protein-1 (LRP1) and receptor for advanced glycation end products (RAGE), respectively. In normal human plasma a soluble form of LRP1 (sLRP1) is a major endogenous brain Aβ 'sinker' that sequesters some 70 to 90 % of plasma Aβ peptides. In Alzheimer's disease (AD), the levels of sLRP1 and its capacity to bind Aβ are reduced which increases free Aβ fraction in plasma. This in turn may increase brain Aβ burden through decreased Aβ efflux and/or increased Aβ influx across the BBB. In Aβ immunotherapy, anti-Aβ antibody sequestration of plasma Aβ enhances the peripheral Aβ 'sink action'. However, in contrast to endogenous sLRP1 which does not penetrate the BBB, some anti-Aβ antibodies may slowly enter the brain which reduces the effectiveness of their sink action and may contribute to neuroinflammation and intracerebral hemorrhage. Anti-Aβ antibody/Aβ immune complexes are rapidly cleared from brain to blood via FcRn (neonatal Fc receptor) across the BBB. In a mouse model of AD, restoring plasma sLRP1 with recombinant LRP-IV cluster reduces brain Aβ burden and improves functional changes in cerebral blood flow (CBF) and behavioral responses, without causing neuroinflammation and/or hemorrhage. The C-terminal sequence of Aβ is required for its direct interaction with sLRP and LRP-IV cluster which is completely blocked by the receptor-associated protein (RAP) that does not directly bind Aβ. Therapies to increase LRP1 expression or reduce RAGE activity at the BBB and/or restore the peripheral Aβ 'sink' action, hold potential to reduce brain Aβ and inflammation, and improve CBF and functional recovery in AD models, and by extension in AD patients.

CNS Neurol Disord Drug Targets. 2009 March ; 8(1): 16–30.

Clearance of amyloid-β peptide across the blood-brain barrier: Implication for therapies in Alzheimer's disease

R Deane, RD Bell, A Sagare, and BV Zlokovic

Aumentar expresión LRP-1 o reducir Actividad RAGE

The main receptors for amyloid-beta peptide (Aβ) transport across the blood-brain barrier (BBB) from brain to blood and blood to brain are low-density lipoprotein receptor related protein-1 (LRP1) and receptor for advanced glycation end products (RAGE), respectively. In normal human plasma a soluble form of LRP1 (sLRP1) is a major endogenous brain Aβ 'sinker' that sequesters some 70 to 90 % of plasma Aβ peptides. In Alzheimer's disease (AD), the levels of sLRP1 and its capacity to bind Aβ are reduced which increases free Aβ fraction in plasma. This in turn may increase brain Aβ burden through decreased Aβ efflux and/or increased Aβ influx across the BBB. In Aβ immunotherapy, anti-Aβ antibody sequestration of plasma Aβ enhances the peripheral Aβ 'sink action'. However, in contrast to endogenous sLRP1 which does not penetrate the BBB, some anti-Aβ antibodies may slowly enter the brain which reduces the effectiveness of their sink action and may contribute to neuroinflammation and intracerebral hemorrhage. Anti-Aβ antibody/Aβ immune complexes are rapidly cleared from brain to blood via FcRn (neonatal Fc receptor) across the BBB. In a mouse model of AD, restoring plasma sLRP1 with recombinant LRP-IV cluster reduces brain Aβ burden and improves functional changes in cerebral blood flow (CBF) and behavioral responses, without causing neuroinflammation and/or hemorrhage. The C-terminal sequence of Aβ is required for its direct interaction with sLRP and LRP-IV cluster which is completely blocked by the receptor-associated protein (RAP) that does not directly bind Aβ. Therapies to increase LRP1 expression or reduce RAGE activity at the BBB and/or restore the peripheral Aβ 'sink' action, hold potential to reduce brain Aβ and inflammation, and improve CBF and functional recovery in AD models, and by extension in AD patients.

CNS Neurol Disord Drug Targets. 2009 March ; 8(1): 16–30.

Obesidad

- **Vínculo entre obesidad y riesgo de demencia. La obesidad durante la edad mediana (de 40 a 45 años) se asocia a un aumento del riesgo de demencia 30 años después.**
- **Las personas con un IMC 30 o más tenían una probabilidad un 75% mayor de desarrollar demencia en comparación con un IMC normal.**
- **La obesidad abdominal va más estrechamente asociada al riesgo de demencia que la obesidad repartida por todo el organismo.**

Whitmer RA, et al. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. BMJ 2005; 330: 1360.

Association of Adiposity Status and Changes in Early to Mid-Adulthood With Incidence of Alzheimer's Disease

Am J Epidemiol 2008;168:1179–1189

Ojo con el peso entre los 30-45 añosiii

Adiposity status and change are potential risk factors for Alzheimer's disease (AD). The authors used data on 2,322 participants in the Baltimore Longitudinal Study of Aging to analyze the relation between AD incidence and adiposity in Cox proportional hazards models, with adjustment for sociodemographic factors and smoking status. Body mass index (BMI; weight (kg)/height $(m)^2$) and waist circumference at specific ages were predicted by empirical Bayes estimators from mixed-effects regression models. After a median of 23.4 years of follow-up between 1958 and 2006, 187 participants developed AD. Among men, being underweight (BMI $\leq$18.5) at age 30, 40, or 45 years increased the likelihood of AD (hazard ratio (HR) = 5.76, 95% confidence interval (CI): 2.07, 16.00); among women, being obese (BMI $\geq$30) at age 30, 40, or 45 years and jointly centrally obese (waist circumference $\geq$80th percentile) at age 30, 35, or 50 years increased AD risk (HR = 6.57, 95% CI: 1.96, 22.02). Women who lost weight (BMI change <10th percentile) between ages 30 and 45 years were also at increased risk (HR = 2.02, 95% CI: 1.06, 3.85). Weight gain among men (BMI change >90th percentile) between ages 30 and 50 years increased AD risk (HR = 3.70, 95% CI: 1.43, 9.56). Future studies should identify age- and gender-specific optimal weights and weight-loss strategies for preventing AD and investigate potential mechanisms.

ORIGINAL CONTRIBUTION

The Metabolic Syndrome and Alzheimer Disease

George Razay, MD, MRCP, FRACP; Anthea Vreugdenhil, PhD; Gordon Wilcock, DM, FRCP

No solo DM sino SDME METABOLICO

Background: The metabolic syndrome is a risk factor for cardiovascular diseases, which have been linked to Alzheimer disease. However, a link between Alzheimer disease and the metabolic syndrome has not yet been established.

Objective: To investigate the relationship between the metabolic syndrome and Alzheimer disease.

Design, Setting, and Participants: Case-control study of 50 consecutive patients diagnosed with probable Alzheimer disease from the Memory Disorders Clinics, Launceston, Australia, and Bristol, England, and 75 cognitively normal controls.

Main Outcome Measures: The odds ratio of the metabolic syndrome as defined by the National Cholesterol Education Program Adult Treatment Panel III.

Results: Compared with controls, patients with Alzheimer disease had a significantly larger mean waist circumference, higher mean plasma concentrations of triglycerides and glucose, and a lower mean plasma concentration of high-density lipoprotein cholesterol, but they had lower mean systolic blood pressure. The metabolic syndrome was associated with Alzheimer disease (odds ratio, 3.2; 95% confidence interval, 1.2-8.4; $P=.02$), and this association was strengthened when the hypertension component was excluded (odds ratio, 7.0; 95% confidence interval, 2.7-18.3; $P<.001$). All of the analyses were adjusted for age, sex, and location.

Conclusions: This study suggests that Alzheimer disease is associated with the metabolic syndrome. This could have implications for the prevention and treatment of Alzheimer disease.

Arch Neurol. 2007;64:93-96

Age and Ageing 2010; **39:** 8–10
doi: 10.1093/ageing/afp211
Published electronically 16 November 2009

COMMENTARY

Pathophysiology of cognitive dysfunction in older people with type 2 diabetes: vascular changes or neurodegeneration?

COEXISTENCIA

HIROYUKI UMEGAKI

Department of Geriatrics, Nagoya University Graduate School of Medicine, 65-Tsuruma-cho, Showa-ku, Nagoya, Aichi, 466-8550, Japan. Email: umegaki@med.nagoya-u.ac.jp

Abstract

Recent studies have revealed that type 2 diabetes mellitus (T2DM) is a risk factor for cognitive dysfunction or dementia, especially those related to Alzheimer's disease (AD). Basic research suggests that insulin accelerates Alzheimer-related pathology through its effects on the amyloid beta (Aβ). Several pathological studies with autopsy samples have demonstrated, however, that dementia subjects with diabetes have less AD-related neuropathology than subjects without diabetes. We and others have reported that small vessel diseases affect cognitive function in older diabetics. Asymptomatic ischemic lesions in T2DM subjects may lower the threshold for the development of dementia and this may explain the inconsistency between the basic research and clinicopathological studies. Longitudinal follow-up of T2DM subjects without overt dementia using both amyloid imaging and magnetic resonance imaging may elucidate these issues. Following up until the development of overt dementia would make it possible to compare both amyloid load and ischemic lesions before and after the development of dementia. Moreover, amyloid imaging in non-demented older people with or without insulin resistance would verify the role of insulin in the processing and deposition of Aβ. Vascular risk factors may represent a therapeutic target, while neurodegenerative pathologies have not yet been amenable to treatment. It remains to be investigated whether medical interventions on vascular risk factors have protective effects against the development and progress of dementia.

¿Es la DM un factor de riesgo para EA?

2. ¿Existe una explicación fisiopatológica?

SI

Pero……

Deben seguir los estudiosiiiiiiiiiii

Diabetes-accelerated memory dysfunction via cerebrovascular inflammation and Aβ deposition in an Alzheimer mouse model with diabetes

7036–7041 | PNAS | April 13, 2010 | vol. 107 | no. 15

EXACERBATION OF POSTSTROKE DEMENTIA BY TYPE 2 DIABETES IS ASSOCIATED WITH SYNERGISTIC INCREASES OF β-SECRETASE ACTIVATION AND β-AMYLOID GENERATION IN RAT BRAINS

Neuroscience 161 (2009) 1045–1056

¿Es la DM un factor de riesgo para EA?

3. ¿Un buen control metabólico se asocia un mejor rendimiento cognitivo?

¿Un buen control metabolico nos dará un mejor rendimiento cognitivo?

- **Se ha descrito que el control glicemico a corto plazo favorece la cognición en el paciente anciano diabético.**

- **Así se ha demostrado una mejora moderada en la memoria de aprendizaje y parcial en habilidades complejas motoras a las tres semanas del control de las glicemias con ADOs o insulinas.**

Araki et al. Geriatr Gerontol Int 2004; 4: 206-12.

Grandman et al. J Am Geritr Soc 1993, 41: 1305-12.

Diabetes as a Risk Factor for Cognitive Decline in Older Patients

Dement Geriatr Cogn Disord 2009;27:24–33

S. Maggi[a] F. Limongi[a] M. Noale[a] G. Romanato[a] P. Tonin[c] R. Rozzini[d]

At baseline, diabetic women had significantly worse scores on all cognitive tests compared to nondiabetic women, but did not show worsening over time, whereas men with diabetes did not show worse scores on cognitive tests at baseline compared to nondiabetic males; however, diabetes in men was associated with a risk of cognitive decline over time, particularly in attention. Higher levels of HbA_{1c} were associated with poorer performance on memory tests at follow-up in both sexes. ***Conclusion:*** The impact of diabetes on cognitive status might differ in older men and women, probably because of a survival effect, with a higher mortality at a younger age among diabetic men. The metabolic and cardiovascular abnormalities associated with diabetes might be responsible for the cognitive decline, at different rates and ages, in men and women. The routine assessment of diabetes complications in the elderly should include cognitive evaluation in both sexes.

5632 participantes, edad media 71 años

A valores más altos HbA1c peor rendimiento cognitivo

Linking Glycemic Control and Executive Function in Rural Older Adults with Diabetes Mellitus

Ha T. Nguyen, PhD, Joseph G. Grzywacz, PhD,* Thomas A. Arcury, PhD,**

OBJECTIVES: To examine the association between glycemic control and the executive functioning domain of cognition and to identify risk factors for inadequate glycemic control that may explain this relationship.

DESIGN: Cross-sectional study.

SETTING: In-person interviews conducted in participants' homes.

PARTICIPANTS: Ninety-five rural older African Americans, American Indians, and whites with diabetes mellitus (DM) from three counties in south-central North Carolina.

MEASUREMENTS: Participants underwent uniform evaluations. Glycemic control was measured using a validated method, and executive function was assessed using a previously established set of measures and scoring procedure. Information pertaining to medication for treatment of DM, knowledge of DM, and DM self-care behaviors were obtained.

RESULTS: In linear regression models adjusting for sex, age, education, ethnicity, duration of DM, and depressive symptoms, executive function was significantly associated with glycemic control. A 1-point higher executive function score was associated with a 0.47 lower glycosylated hemoglobin value ($P = .01$). The association between glycemic control and executive function became nonsignificant ($P = .08$) when controlling for several glycemic control risk factors, including use of DM medication and DM knowledge.

CONCLUSION: These results suggest that poor glycemic control is associated with impairments in performance on composite measures of executive function and that modifiable risk factors for glycemic control such as use of DM medication and DM knowledge may explain this relationship. J Am Geriatr Soc 58:1123–1127, 2010.

A valores más altos de Hb A1 mayor dificultad para realizar funciones ejecutivas

The Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes Study (ACCORD-MIND): Rationale, Design, and Methods

Jeff D. Williamson, MD, MHS,[a,b] Michael E. Miller, PhD,[b] R. Nick Bryan, MD, PhD,[d]

The American Journal of Cardiology (www.AJConline.org) Vol 99 (12A) June 18, 2007

http://clinicaltrials.gov/ct2/show/NCT00182910

Hypoglycemic Episodes and Risk of Dementia in Older Patients With Type 2 Diabetes Mellitus

Conclusions Among older patients with type 2 diabetes, a history of severe hypoglycemic episodes was associated with a greater risk of dementia. Whether minor hypoglycemic episodes increase risk of dementia is unknown.

JAMA. 2009;301(15):1565-1572 www.jama.com

DAÑO NEURONAL

Cognitive Function in Type 1 Diabetic Adults With Early Exposure to Severe Hypoglycemia

A 16-year follow-up study

RESEARCH DESIGN AND METHODS — Sixteen years subsequent to a study of cognitive function in 28 diabetic children and 28 matched control subjects, we reexamined the same subjects with a 96% participation rate. Diabetic subjects were classified as with (n = 9) or without (n = 18) early (≤10 years of age) SH, which was defined as convulsions or loss of consciousness.

RESULTS — Overall, cognitive scores were 0.9 SDs lower in subjects with early SH compared with subjects without early SH (P = 0.003). The two diabetic groups particularly differed with respect to problem solving, verbal function, and psychomotor efficiency. Earlier age at first incident of SH was associated with poorer cognition (P for trend = 0.001).

CONCLUSIONS — The findings suggest that early exposure to SH may have lasting and clinically relevant effects on cognition.

Diabetes Care 33:1945–1947, 2010

CUANTO ANTES SE TENGAN LAS HIPOGLICEMIAS----PEOR

Relationships Between Daily Acute Glucose Fluctuations and Cognitive Performance Among Aged Type 2 Diabetic Patients

RESULTS — MAGE was significantly correlated with MMSE ($r = 0.83$; $P < 0.001$) and with cognition composite score ($r = 0.68$; $P < 0.001$). Moreover, MAGE was associated with the MMSE ($P < 0.001$) and cognition composite score ($P < 0.001$) independently of age, sex, BMI, waist-to-hip (WHR) ratio, drug intake, physical activity, mean arterial blood pressure, FPG, PPG, and A1C.

CONCLUSIONS — MAGE during a daily period was associated with an impairment of cognitive functioning independent of A1C, FPG, and PPG. The present data suggest that interventional trials in older patients with type 2 diabetes should target not only A1C, PPG, and FPG but also daily acute glucose swings.

Diabetes Care 33:2169–2174, 2010

OJO con:
la amplitud media de las desviaciones de la glucemia

¿Cómo alcanzar el control?

The New England
Journal of Medicine

VOLUME 346 FEBRUARY 7, 2002 NUMBER 6

REDUCTION IN THE INCIDENCE OF TYPE 2 DIABETES WITH LIFESTYLE INTERVENTION OR METFORMIN

DIABETES PREVENTION PROGRAM RESEARCH GROUP*

Conclusions Lifestyle changes and treatment with metformin both reduced the incidence of diabetes in persons at high risk. The lifestyle intervention was more effective than metformin. (N Engl J Med 2002; 346:393-403.)

EL EJERCICIO SABEMOS QUE TAMBIEN ES BUENO PARA MEJORAR RENDIMIENTO COGNITIVO

Improving Metabolic Control Leads to Better Working Memory in Adults With Type 2 Diabetes

Mejora en cognición con mejor control DM

RESULTS — Pretreatment fasting plasma glucose (FPG) in both groups was similar, and after 24 weeks both treatment groups showed similar significant reductions in FPG (2.1–2.3 mmol/l). Working memory improved with both rosiglitazone ($P < 0.001$) and glyburide ($P = 0.017$). Improvement (25–31% reduction in errors) was most evident on the Paired Associates Learning Test and was significantly correlated ($r = 0.30$) with improved glycemic control as measured by FPG.

CONCLUSIONS — Similar and statistically significant cognitive improvement was observed with both rosiglitazone and glyburide therapy, and the magnitude of this effect was correlated with the degree to which FPG improved. These results suggest that a cognitive benefit is achievable with pharmacological interventions targeting glycemic control.

Diabetes Care 29:345–351, 2006

¿Efecto fármaco?

¿Efecto fármaco?

Antidiabetic drug metformin (Glucophage^{R}) increases biogenesis of Alzheimer's amyloid peptides via up-regulating *BACE1* transcription

PNAS | March 10, 2009 | vol. 106 | no. 10 | 3907–3912

Incremento producción BA a traves de B-secretasa.
Necesidad de replica.
Comprobar en humanos

Brazo metformina de la DPPOS
Phase II: NCT00620191

¿Efecto fármaco?

Tiazolidinadionas (glitazonas).

Agonistas PPAR gamma (efecto neuroprotector) además de aumentar la sensibilidad a la insulina.

PIOGLITAZONE IMPROVED COGNITION IN A PILOT STUDY ON PATIENTS WITH ALZHEIMER'S DISEASE AND MILD COGNITIVE IMPAIRMENT WITH DIABETES MELLITUS

JAGS JANUARY 2009–VOL. 57, NO. 1

doi:10.1093/brain/awh452 *Brain* (2005), **128**, 1442–1453

Acute treatment with the PPARγ agonist pioglitazone and ibuprofen reduces glial inflammation and Aβ1–42 levels in APPV717I transgenic mice

¿Efecto fármaco?

Tiazolidinadionas (glitazonas).

Rosiglitazone Effects to Ameliorate Alzheimer's Disease Pathogenic Features: Insulin Signaling and Neurotrophic Factors

J Neuropsychiatry Clin Neurosci 21:3, Summer 2009

M E Risner. Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease. The Pharmacogenomics Journal (2006) 6, 246–254.

Efecto 8 mg en personas no Apo E4

Complete Rescue of Cerebrovascular Function in Aged Alzheimer's Disease Transgenic Mice by Antioxidants and Pioglitazone, a Peroxisome Proliferator-Activated Receptor γ Agonist

The Journal of Neuroscience, September 10, 2008 · 28(37):9287–9296 · 9287

Rosiglitazone and Cognitive Stability in Older Individuals With Type 2 Diabetes and Mild Cognitive Impairment

RESEARCH DESIGN AND METHODS — A total of 97 older individuals (mean ± SD age 76 ± 6 years) who had recently (<2 months) started an antidiabetes treatment of metformin (500 mg twice a day) (n = 30) or metformin (500 mg/day)+rosiglitazone (4 mg/day) (n = 32) or diet (n = 35) volunteered. The neuropsychological test battery consisted of the Mini-Mental State Examination (MMSE), Rey Verbal Auditory Learning Test (RAVLT) total recall, and Trail Making Tests (TMT-A and TMT-B) performed at baseline and every 12 weeks for 36 weeks along with clinical testing.

CONCLUSIONS — Rosiglitazone may protect against cognitive decline in older individuals with type 2 diabetes and MCI.

Diabetes Care 33:1706–1711, 2010

¿Efecto fármaco?

The Rosiglitazone effects on Cognition for adults in later Life (RECALL; NCT00242593).

Estimated Primary Completion Date:July 2010 (Final data collection date for primary outcome measure)

The Pioglitazone or exercise to treat Mild Cognitive Impairment (POEM; NCT00736996).

Estimated Primary Completion Date: August 2011 (Final data collection date for primary outcome measure)

Comprobar en humanos

¿Efecto fármaco?

Las incretinas, fármacos muy prometedores

J Alzheimers Dis. 2010 January ; 19(4): 1205–1219. doi:10.3233/JAD-2010-1314.

GLP-1 Receptor Stimulation Reduces Amyloid-β Peptide Accumulation and Cytotoxicity in Cellular and Animal Models of Alzheimer's Disease

Holscher C. Incretin analogues that have been developed to treat type 2 diabetes hold promise as a novel treatment strategy for Alzheimer's disease. Recent Pat CNS Drug Discov. 2010; 5: 109-17.

Comprobar en humanos

¿Es la DM un factor de riesgo para EA?

3. **¿Un buen control metabólico se asocia un mejor rendimiento cognitivo?**

SI

Pero……

¿Es la DM un factor de riesgo para EA?

4. **¿Los profesionales que atienden pacientes con DM deben explorar la cognición?**

Aumentar la alerta

- **Frecuentemente la demencia no esta diagnosticada, especialmente en los estadíos iniciales.**

- **Debe evalúarse de manera especifica la cognición en aquellas personas con DM y que:**
  - **-Fallen en tomar el tto correctamente.**
  - **-Tengan frecuentes episodios de hipoglicemia.**
  - **- Malos controles glicemicios sin una explicación pausible.**

Gregg EW. Complications of diabetes in elderly people. Underestimated problems include cognitive decline and physical disability. BMJ 2002b; 325,916-7

Aumentar la alerta

Assessment of cognitive status in patients with type 2 diabetes through the mini-mental status examination: a cross-sectional study

Renata C Alencar*, Roberta A Cobas, Marília B Gomes

Diabetology & Metabolic Syndrome 2010, **2**:10

Conclusions: We conclude that patients with type 2 diabetes should be regularly evaluated for their cognitive function, because duration of disease could be associated with decline in cognition. The early implementation of mini mental which is a simple method of execution can be done to detect early stages of dementia. This test could be an important tool to access the ability of patient to understand their disease and treatment.

INCORPORAR EL MINIMENTAL TEST A LA EXPLORACION ANUAL

ATENTOS A LA IMPORTANTE COMORBILIDAD

ORIGINALES

Aspectos de comorbilidad en pacientes ancianos con demencia. Diferencias por edad y género

F. Formiga[a], I. Fort[b], M. J. Robles[c], E. Barranco[d], M. C. Espinosa[e] y S. Riu[f], del Grupo de trabajo de demencia de la Sociedad Catalana de Geriatría y Gerontología

Fundamento y objetivo. La prevalencia de demencia en pacientes ancianos es alta. El objetivo del estudio es evaluar algunos aspectos de comorbilidad en los pacientes con demencia. Además se explora si existen diferencias según la edad (mayores o no de 84 años) y el género de los pacientes.

Pacientes y métodos. Se evaluaron prospectivamente 311 pacientes mayores de 64 años con demencia. Se recogieron variables sociodemográficas, el tipo de demencia, el índice de Barthel (IB), el índice de Lawton (IL), el *Mini Mental State Examination* (MMSE), el índice de Charlson, el número total de medicamentos, los antecedentes de hipertensión (HTA), diabetes (DM), dislipidemia (DL), insuficiencia cardíaca (IC), enfermedad pulmonar obstructiva crónica (EPOC) y neoplasia.

Resultados. Se trataba de 222 mujeres (71,4%) y 89 varones, con una edad media (desviación estándar [DE]) de 80,6 (6) años. La media del número total de medicamentos fue de 5,8 (2,6). La media del índice de Charlson fue de 2,1 (1,3). Existía en el 51% de los casos HTA, en 24% DM, en 24% DL, en 13% IC, en 11% EPOC y en el 8% neoplasia. Respecto al género, destacaba mejor puntuación en el MMSE, mayor comorbilidad, mayor porcentaje de casados y mayor prevalencia de demencia vascular en hombres en comparación con las mujeres, donde había mayor presencia de enfermedad de Alzheimer y mayor porcentaje de viudas. En relación a la edad había mayor número de viudos, peor IL, más IC y menos DL en los mayores de 84 años.

Conclusiones. Los pacientes ancianos con demencia tienen una alta comorbilidad y un importante consumo de fármacos de prescripción crónica. Existen variaciones en la comorbilidad según la edad y el género, que deben tenerse en cuenta.

Uno de cada cuatro, era DM en tto farmacológico.

Antipsychotic Drug[illegible]nd Hyperglycemia in Older [illegible] Diabetes

Lorraine L[illegible]harm, PhD; Andrea Gruneir, PhD; Hadas D. Fischer, MD; Da[illegible]D, MSc; Nathan Herrmann, MD; Janet E. Hux, MD, MSc;

Se evalúan 13817 diabéticos después de iniciar tto con antipsicóticos. El 11% precisaron hospitalización por hiperglicemia.

B[illegible]

ci[illegible]

bet[illegible]

mia[illegible]yce-[illegible]es.

Meth[illegible]-control design and population-[illegible]abases in Ontario, Canada, persons ag[illegible]ars or older with diabetes who started treatment with an antipsychotic drug from April 1, 2002, to March 31, 2006, were followed up from treatment start until March 31, 2007. The cohort was subdivided into 3 groups: insulin-treated, oral hypoglycemic agent only–treated, and no diabetes treatment. We defined cases as patients hospitalized (emergency department visit or hospital admissions) for hyperglycemia. Each case was matched with up to 10 controls. We compared the likelihood of hyperglycemia among current users of atypical and typical antipsychotic agents with that among remote antipsychotic users (discontinued >180 days), based on prescriptions closest to event date.

Results: Of 13 817 patients studied, 1515 (11.0%) were hospitalized for hyperglycemia. Current antipsychotic treatment was associated with a higher risk of hyperglycemia compared with remote antipsychotic use in all diabetes treatment groups (overall adjusted rate ratio, 1.50; 95% confidence interval, 1.29-1.74). The risk was increased among patients who were treated with atypical and typical antipsychotic agents and was extremely high among patients who were just starting treatment (only 1 prescription before event).

Conclusions: Among older patients with diabetes, the initiation of treatment with antipsychotic drugs was associated with a significantly increased risk of hospitalization for hyperglycemia ($P<.001$). The risk was particularly high during the initial course of treatment and was increased with the use of all antipsychotic agents.

Arch Intern Med. 2009;169(14):1282-1289

¿Es la DM un factor de riesgo para EA?

3. **¿Los profesionales que atienden pacientes con DM deben explorar la cognición?**

SI

Mensajes para casa

- La insulina y los receptores de insulina son vitales a la hora de aprender y de manejar la memoria.
- Parece existir una asociación no casual entre DM (obesidad e hiperinsulinemia) y demencia. Evidente para D.vascular pero tambien para EA.
- Exsten unos mecanismos fisiopatológicos que pueden explicar la asociación entre DM y EA. La DM predispone a tener EA en un subgrupo de pacientes con DM.

Mensajes para casa

- La EA podría estar condicionada, al menos en parte, por una resistencia cerebral a la insulina, una especie de diabetes cerebral (tipo 3 ??).
- En la DM también existe un transtorno del metabolismo de las HDL que interfiere en la retirada de amiloide del cerebro.
- Un peor control metabólico comportará un menor rendimiento cognitivo. ¿Efecto fármaco?
- Debe explorarse la cognición en los pacientes con DM.