



UNIVERSITAT DE
BARCELONA

Efecto del síndrome metabólico provocado por una dieta rica en grasa en ratones APP^{swe}/PS1^{dE9}, modelo experimental de la enfermedad de Alzheimer, y posibles terapias farmacológicas

Miren Ettcheto Arriola

ADVERTIMENT. La consulta d'aquesta tesi queda condicionada a l'acceptació de les següents condicions d'ús: La difusió d'aquesta tesi per mitjà del servei TDX (www.tdx.cat) i a través del Dipòsit Digital de la UB (diposit.ub.edu) ha estat autoritzada pels titulars dels drets de propietat intel·lectual únicament per a usos privats emmarcats en activitats d'investigació i docència. No s'autoritza la seva reproducció amb finalitats de lucre ni la seva difusió i posada a disposició des d'un lloc aliè al servei TDX ni al Dipòsit Digital de la UB. No s'autoritza la presentació del seu contingut en una finestra o marc aliè a TDX o al Dipòsit Digital de la UB (framing). Aquesta reserva de drets afecta tant al resum de presentació de la tesi com als seus continguts. En la utilització o cita de parts de la tesi és obligat indicar el nom de la persona autora.

ADVERTENCIA. La consulta de esta tesis queda condicionada a la aceptación de las siguientes condiciones de uso: La difusión de esta tesis por medio del servicio TDR (www.tdx.cat) y a través del Repositorio Digital de la UB (diposit.ub.edu) ha sido autorizada por los titulares de los derechos de propiedad intelectual únicamente para usos privados enmarcados en actividades de investigación y docencia. No se autoriza su reproducción con finalidades de lucro ni su difusión y puesta a disposición desde un sitio ajeno al servicio TDR o al Repositorio Digital de la UB. No se autoriza la presentación de su contenido en una ventana o marco ajeno a TDR o al Repositorio Digital de la UB (framing). Esta reserva de derechos afecta tanto al resumen de presentación de la tesis como a sus contenidos. En la utilización o cita de partes de la tesis es obligado indicar el nombre de la persona autora.

WARNING. On having consulted this thesis you're accepting the following use conditions: Spreading this thesis by the TDX (www.tdx.cat) service and by the UB Digital Repository (diposit.ub.edu) has been authorized by the titular of the intellectual property rights only for private uses placed in investigation and teaching activities. Reproduction with lucrative aims is not authorized nor its spreading and availability from a site foreign to the TDX service or to the UB Digital Repository. Introducing its content in a window or frame foreign to the TDX service or to the UB Digital Repository is not authorized (framing). Those rights affect to the presentation summary of the thesis as well as to its contents. In the using or citation of parts of the thesis it's obliged to indicate the name of the author.

BIBLIOGRAFÍA

BIBLIOGRAFÍA

A

Alafuzoff, I., Overmyer, M., Helisalmi, S., & Soininen, H. (2000). Lower Counts of Astroglia and Activated Microglia in Patients with Alzheimer's Disease with Regular Use of Non-Steroidal Anti-Inflammatory Drugs. *Journal of Alzheimer's Disease: E* 2(1), 37–46.

Alberti, K. G. M. M., & Zimmet, P. Z. (1998). Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO Consultation. *Diabetic Medicine*, 15(7), 539–553.

Albin, R. L., & Greenamyre, J. T. (1992). Alternative excitotoxic hypotheses. *Neurology*, 42(4), 733–8.

Ali, M. A., El-Abhar, H. S., Kamel, M. A., & Attia, A. S. (2015). Antidiabetic Effect of Galantamine: Novel Effect for a Known Centrally Acting Drug. *PloS One*, 10(8), e0134648.

Alley, G. M., Bailey, J. A., Chen, D., Ray, B., Puli, L. K., Tanila, H., ... Lahiri, D. K. (2010). Memantine lowers amyloid-beta peptide levels in neuronal cultures and in APP/PS1 transgenic mice. *Journal of Neuroscience Research*, 88(1), 143–54.

Alzheimer's association. (2014) Alzheimer's disease facts and figures. *Alzheimer's Dementia*, 10(2):e47–92. Recuperado de <http://linkinghub.elsevier.com/retrieve/pii/S1552526014000624>

Arriagada, P. V *et al.* (1992) 'Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease.', *Neurology*, 42(3 Pt 1), pp. 631–9.

Arrieta-Cruz, I., & Gutiérrez-Juárez, R. (2016). The role of insulin resistance and glucose metabolism dysregulation in the development of Alzheimer's disease. *Revista de Investigacion Clinica*, 68(2), 53–58.

Arrieta-Cruz, I., Knight, C. M., & Gutiérrez-Juárez, R. (2015). Acute Exposure of the Mediobasal Hypothalamus to Amyloid- β 25-35 Perturbs Hepatic Glucose Metabolism. *Journal of Alzheimer's Disease*, 46(4), 843–848.

Arterburn, D. E., Crane, P. K., & Sullivan, S. D. (2004). The coming epidemic of obesity in elderly Americans. *Journal of the American Geriatrics Society*, 52(11), 1907–12.

Arvanitakis, Z., Wilson, R. S., Bienias, J. L., Evans, D. A., & Bennett, D. A. (2004). Diabetes Mellitus and Risk of Alzheimer Disease and Decline in Cognitive Function. *Archives of Neurology*, 61(5), 661.

Atamna, H., & Frey, W. H. (2007). Mechanisms of mitochondrial dysfunction and energy deficiency in Alzheimer's disease. *Mitochondrion*, 7(5), 297–310.

Austin, S., & St-Pierre, J. (2012). PGC1 α and mitochondrial metabolism--emerging concepts and relevance in ageing and neurodegenerative disorders. *Journal of Cell Science*, 125(Pt 21), 4963–71.

Awad, N., Gagnon, M., & Messier, C. (2004). The Relationship between Impaired Glucose Tolerance, Type 2 Diabetes, and Cognitive Function. *Journal of Clinical and Experimental Neuropsychology*, 26(8), 1044–1080.

B

Banks, W. A. (2006). Denial versus dualism: the blood-brain barrier as an interface of the gut-brain axis. *Endocrinology*, 147(6), 2609–10.

Banks, W. A., Owen, J. B., & Erickson, M. A. (2012). Insulin in the brain: there and back again. *Pharmacology & Therapeutics*, 136(1), 82–93.

Banno, R., Zimmer, D., De Jonghe, B. C., Atienza, M., Rak, K., Yang, W., & Bence, K. K. (2010). PTP1B and SHP2 in POMC neurons reciprocally regulate energy balance in mice. *The Journal of Clinical Investigation*, 120(3), 720–34.

Bartus, R. T., Dean, R. L., Beer, B., & Lippa, A. S. (1982). The cholinergic hypothesis of geriatric memory dysfunction. *Science (New York, N.Y.)*, 217(4558), 408–14.

Basak, J. M., Verghese, P. B., Yoon, H., Kim, J., & Holtzman, D. M. (2012). Low-density lipoprotein receptor represents an apolipoprotein E-independent pathway of A β uptake and degradation by astrocytes. *The Journal of Biological Chemistry*, 287(17), 13959–71.

Bateman, R. J., Munsell, L. Y., Morris, J. C., Swarm, R., Yarasheski, K. E., & Holtzman, D. M. (2006). Human amyloid-beta synthesis and clearance rates as measured in cerebrospinal fluid in vivo. *Nature Medicine*, 12(7), 856–61.

Bekris, L. M., Yu, C.-E., Bird, T. D., & Tsuang, D. W. (2010). Genetics of Alzheimer disease. *Journal of Geriatric Psychiatry and Neurology*, *23*(4), 213–27.

Benedict, C., Hallschmid, M., Hatke, A., Schultes, B., Fehm, H. L., Born, J., & Kern, W. (2004). Intranasal insulin improves memory in humans. *Psychoneuroendocrinology*, *29*(10), 1326–34.

Besseiche, A., Riveline, J.-P., Gautier, J.-F., Bréant, B., & Blondeau, B. (2015). Metabolic roles of PGC-1 α and its implications for type 2 diabetes. *Diabetes & Metabolism*, *41*(5), 347–357.

Biessels, G. J., Kappelle, A. C., Bravenboer, B., Erkelens, D. W., & Gispen, W. H. (1994). Cerebral function in diabetes mellitus. *Diabetologia*, *37*(7), 643–650.

Birks, J., Grimley Evans, J., Iakovidou, V., & Tsolaki, M. (2000). Rivastigmine for Alzheimer's disease. In J. Birks (Ed.), *Cochrane Database of Systematic Reviews* (p. CD001191). Chichester, UK: John Wiley & Sons, Ltd.

Björkhem, I., & Meaney, S. (2004). Brain cholesterol: long secret life behind a barrier. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *24*(5), 806–15.

Block, M. L., Zecca, L., & Hong, J.-S. (2007). Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. *Nature Reviews Neuroscience*, *8*(1), 57–69.

Bonabello, A., Galmozzi, M. R., Canaparo, R., Isaia, G. C., Serpe, L., Muntoni, E., & Zara, G. P. (2003). Dexibuprofen (S+-isomer ibuprofen) reduces gastric

damage and improves analgesic and antiinflammatory effects in rodents. *Anesthesia and Analgesia*, 97(2), 402–8, table of contents.

Bordji, K., Becerril-Ortega, J., & Buisson, A. (2011). Synapses, NMDA receptor activity and neuronal A β production in Alzheimer's disease. *Reviews in the Neurosciences*, 22(3), 285–294.

Brecht, W. J., Harris, F. M., Chang, S., Tesseur, I., Yu, G.-Q., Xu, Q., ... Huang, Y. (2004). Neuron-specific apolipoprotein e4 proteolysis is associated with increased tau phosphorylation in brains of transgenic mice. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 24(10), 2527–34.

Brinton, R. D., Yao, J., Yin, F., Mack, W. J., & Cadenas, E. (2015). Perimenopause as a neurological transition state. *Nature Reviews. Endocrinology*, 11(7), 393–405.

Brookmeyer, R., Johnson, E., Ziegler-Graham, K., & Arrighi, H. M. (2007). Forecasting the global burden of Alzheimer's disease. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, 3(3), 186–91.

Bruce-Keller, A. J., Umberger, G., McFall, R., & Mattson, M. P. (1999). Food restriction reduces brain damage and improves behavioral outcome following excitotoxic and metabolic insults. *Annals of Neurology*, 45(1), 8–15.

Bu, G. (2009). Apolipoprotein E and its receptors in Alzheimer's disease: pathways, pathogenesis and therapy. *Nature Reviews. Neuroscience*, 10(5), 333–344.

Bullock, R., Touchon, J., Bergman, H., Gambina, G., He, Y., Rapatz, G., ... Lane, R. (2005). Rivastigmine and donepezil treatment in moderate to

moderately-severe Alzheimer's disease over a 2-year period. *Current Medical Research and Opinion*, 21(8), 1317–27.

Butterfield, D. A., & Pocernich, C. B. (2003). The glutamatergic system and Alzheimer's disease: therapeutic implications. *CNS Drugs*, 17(9), 641–652.

C

Calsolaro, V., & Edison, P. (2016). Alterations in Glucose Metabolism in Alzheimer's Disease. *Recent Patents on Endocrine, Metabolic & Immune Drug Discovery*, 10(1), 31–39.

Camacho, A., Huang, J. K., Delint-Ramirez, I., Yew Tan, C., Fuller, M., Lelliott, C. J., ... Franklin, R. J. M. (2013). Peroxisome proliferator-activated receptor gamma-coactivator-1 alpha coordinates sphingolipid metabolism, lipid raft composition and myelin protein synthesis. *The European Journal of Neuroscience*, 38(5), 2672–83.

Campos-Peña, V. & Meraz-Ríos, M.A. (2014). Alzheimer Disease: The Role of A β in the Glutamatergic System (Figura). *Neurochemistry, chapter 10*. Recuperado de <https://www.intechopen.com/books/neurochemistry/alzheimer-disease-the-role-of-a-in-the-glutamatergic-system>

Cao, D., Lu, H., Lewis, T. L., & Li, L. (2007). Intake of sucrose-sweetened water induces insulin resistance and exacerbates memory deficits and amyloidosis in a transgenic mouse model of Alzheimer disease. *The Journal of Biological Chemistry*, 282(50), 36275–82.

Cárdenas-Aguayo, M. del C., Cortes-Ortiz, M., Jiménez-Ramos, B., Gómez-Virgilio, L., Ramírez-Rodríguez, G., Vera-Arroyo, E., ... Meraz-Ríos, M.A.

(2014) Physiological Role of Amyloid Beta in Neural Cells: The Cellular Trophic Activity. (Figura). *Neurochemistry, chapter 9*. Recuperado de <https://www.intechopen.com/books/neurochemistry/physiological-role-of-amyloid-beta-in-neural-cells-the-cellular-trophic-activity>

Carroll, J. C., Rosario, E. R., Chang, L., Stanczyk, F. Z., Oddo, S., LaFerla, F. M., & Pike, C. J. (2007). Progesterone and Estrogen Regulate Alzheimer-Like Neuropathology in Female 3xTg-AD Mice. *Journal of Neuroscience*, 27(48), 13357–13365.

Carson, J. A., & Turner, A. J. (2002). Beta-amyloid catabolism: roles for neprilysin (NEP) and other metallopeptidases? *Journal of Neurochemistry*, 81(1), 1–8.

Carter, C. L., Resnick, E. M., Mallampalli, M., & Kalbarczyk, A. (2012). Sex and gender differences in Alzheimer's disease: recommendations for future research. *Journal of Women's Health (2002)*, 21(10), 1018–23.

Carvalho, C., Cardoso, S., Correia, S. C., Santos, R. X., Santos, M. S., Baldeiras, I., ... Moreira, P. I. (2012). Metabolic alterations induced by sucrose intake and Alzheimer's disease promote similar brain mitochondrial abnormalities. *Diabetes*, 61(5), 1234–42.

Caspersen, C., Wang, N., Yao, J., Sosunov, A., Chen, X., Lustbader, J. W., ... Yan, S. Du. (2005). Mitochondrial A : a potential focal point for neuronal metabolic dysfunction in Alzheimer's disease. *The FASEB Journal*, 19(14), 2040–1.

Chang, S., ran Ma, T., Miranda, R. D., Balestra, M. E., Mahley, R. W., & Huang, Y. (2005). Lipid- and receptor-binding regions of apolipoprotein E4 fragments act in concert to cause mitochondrial dysfunction and neurotoxicity.

Proceedings of the National Academy of Sciences of the United States of America, 102(51), 18694–9.

Cheng, A., Wan, R., Yang, J.-L., Kamimura, N., Son, T. G., Ouyang, X., ... Mattson, M. P. (2012). Involvement of PGC-1 α in the formation and maintenance of neuronal dendritic spines. *Nature Communications*, 3, 1250.

Chua, L.-M., Lim, M.-L., Chong, P.-R., Hu, Z. P., Cheung, N. S., & Wong, B.-S. (2012). Impaired neuronal insulin signaling precedes A β 42 accumulation in female A β PPsw/PS1 Δ E9 mice. *Journal of Alzheimer's Disease: JAD*, 29(4), 783–91.

Clarke, J. R., Lyra E Silva, N. M., Figueiredo, C. P., Frozza, R. L., Ledo, J. H., Beckman, D., ... De Felice, F. G. (2015). Alzheimer-associated A β oligomers impact the central nervous system to induce peripheral metabolic deregulation. *EMBO Molecular Medicine*, 7(2), 190–210.

Claxton, A., Baker, L. D., Hanson, A., Trittschuh, E. H., Cholerton, B., Morgan, A., ... Craft, S. (2015). Long-acting intranasal insulin detemir improves cognition for adults with mild cognitive impairment or early-stage Alzheimer's disease dementia. *Journal of Alzheimer's Disease : JAD*, 44(3), 897–906.

Claxton, A., Baker, L. D., Wilkinson, C. W., Trittschuh, E. H., Chapman, D., Watson, G. S., ... Craft, S. (2013). Sex and ApoE genotype differences in treatment response to two doses of intranasal insulin in adults with mild cognitive impairment or Alzheimer's disease. *Journal of Alzheimer's Disease : JAD*, 35(4), 789–97.

Corder, E. H., Saunders, A. M., Strittmatter, W. J., Schmechel, D. E., Gaskell, P. C., Small, G. W., ... Pericak-Vance, M. A. (1993). Gene dose of

apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science (New York, N.Y.)*, 261(5123), 921–3.

Corder, E. H., Woodbury, M. A., Volkman, I., Madsen, D. K., Bogdanovic, N., & Winblad, B. (2000). Density profiles of Alzheimer disease regional brain pathology for the huddinge brain bank: pattern recognition emulates and expands upon Braak staging. *Experimental Gerontology*, 35(6–7), 851–64.

Côté, S., Carmichael, P.-H., Verreault, R., Lindsay, J., Lefebvre, J., & Laurin, D. (2012). Nonsteroidal anti-inflammatory drug use and the risk of cognitive impairment and Alzheimer's disease. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, 8(3), 219–26.

Coyle, J. T., & Puttfarcken, P. (1993). Oxidative stress, glutamate, and neurodegenerative disorders. *Science (New York, N.Y.)*, 262(5134), 689–95.

Crane, P. K., Walker, R., Hubbard, R. A., Li, G., Nathan, D. M., Zheng, H., ... Larson, E. B. (2013). Glucose Levels and Risk of Dementia. *New England Journal of Medicine*, 369(6), 540–548.

Cummings, J., Lee, G., Mortsdorf, T., Ritter, A., & Zhong, K. (2017). Alzheimer's disease drug development pipeline: 2017. *Alzheimer's & Dementia (New York, N. Y.)*, 3(3), 367–384.

Czeh, M., Gressens, P., & Kaindl, A. M. (2011). The yin and yang of microglia. *Developmental Neuroscience*, 33(3-4), 199–209.

D

Daneman, D. (2006). Type 1 diabetes. *The Lancet*, 367(9513), 847–858.

Deane, R., Sagare, A., & Zlokovic, B. V. (2008). The role of the cell surface LRP and soluble LRP in blood-brain barrier Abeta clearance in Alzheimer's disease. *Current Pharmaceutical Design*, 14(16), 1601–5.

Deakin, J. F. (1983). Alzheimer's disease: recent advances and future prospects. *British Medical Journal (Clinical Research Ed.)*, 287(6402), 1323–4.

De Felice, F. G., Lourenco, M. V., & Ferreira, S. T. (2014). How does brain insulin resistance develop in Alzheimer's disease? *Alzheimer's & Dementia : The Journal of the Alzheimer's Association*, 10(1 Suppl), S26-32.

Delacourte, A., & Defossez, A. (1986). Alzheimer's disease: Tau proteins, the promoting factors of microtubule assembly, are major components of paired helical filaments. *Journal of the Neurological Sciences*, 76(2–3), 173–86.

De la Monte, S. M., & Wands, J. R. (2005). Review of insulin and insulin-like growth factor expression, signaling, and malfunction in the central nervous system: relevance to Alzheimer's disease. *Journal of Alzheimer's Disease : JAD*, 7(1), 45–61.

De la Monte, S. M. (2009). Insulin resistance and Alzheimer's disease. *BMB Reports*, 42(8), 475–81.

Di Cairano, E. S., Davalli, A. M., Perego, L., Sala, S., Sacchi, V. F., La Rosa, S., ... Perego, C. (2011). The glial glutamate transporter 1 (GLT1) is expressed by pancreatic beta-cells and prevents glutamate-induced beta-cell death. *The Journal of Biological Chemistry*, 286(16), 14007–18.

Dineley, K. T., Jahrling, J. B., & Denner, L. (2014). Insulin resistance in Alzheimer's disease. *Neurobiology of Disease*, 72 Pt A, 92–103.

Dou, J.-T., Chen, M., Dufour, F., Alkon, D. L., & Zhao, W.-Q. (2005). Insulin receptor signaling in long-term memory consolidation following spatial learning. *Learning & Memory (Cold Spring Harbor, N.Y.)*, 12(6), 646–55.

Du, H., Guo, L., Zhang, W., Rydzewska, M., & Yan, S. (2011). Cyclophilin D deficiency improves mitochondrial function and learning/memory in aging Alzheimer disease mouse model. *Neurobiology of Aging*, 32(3), 398–406.

E

Eckert, A., Schmitt, K., & Götz, J. (2011). Mitochondrial dysfunction - the beginning of the end in Alzheimer's disease? Separate and synergistic modes of tau and amyloid- toxicity. *Alzheimer's Research & Therapy*, 3(2), 15.

Edison, P., Archer, H. A., Hinz, R., Hammers, A., Pavese, N., Tai, Y. F., ... Brooks, D. J. (2007). Amyloid, hypometabolism, and cognition in Alzheimer disease: an [11C]PIB and [18F]FDG PET study. *Neurology*, 68(7), 501–8.

Eisele, Y. S., Obermüller, U., Heilbronner, G., Baumann, F., Kaeser, S. A., Wolburg, H., ... Jucker, M. (2010). Peripherally applied Abeta-containing inoculates induce cerebral beta-amyloidosis. *Science (New York, N.Y.)*, 330(6006), 980–2.

Erickson, M. A., & Banks, W. A. (2013). Blood-brain barrier dysfunction as a cause and consequence of Alzheimer's disease. *Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism*, 33(10), 1500–13.

Ettcheto, M., Petrov, D., Pedrós, I., de Lemos, L., Pallàs, M., Alegret, M., ... Camins, A. (2015). Hypercholesterolemia and neurodegeneration.

Comparison of hippocampal phenotypes in LDLr knockout and APP^{swe}/PS1^{dE9} mice. *Experimental Gerontology*, 65, 69–78.

F

Farina, C., Aloisi, F., & Meinl, E. (2007). Astrocytes are active players in cerebral innate immunity. *Trends in Immunology*, 28(3), 138–145.

Farrer, L. A., Cupples, L. A., Haines, J. L., Hyman, B., Kukull, W. A., Mayeux, R., ... van Duijn, C. M. (1997). Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *JAMA*, 278(16), 1349–56.

Fernández Martínez, M., Castro Flores, J., Pérez de las Heras, S., Mandaluniz Lekumberri, A., Gordejuela Menocal, M., & Zarranz Imirizaldu, J. J. (2008). Risk factors for dementia in the epidemiological study of Mungualde County (Basque Country-Spain). *BMC Neurology*, 8(1), 39.

Ferreira, S. T., Clarke, J. R., Bomfim, T. R., & De Felice, F. G. (2014). Inflammation, defective insulin signaling, and neuronal dysfunction in Alzheimer's disease. *Alzheimer's & Dementia*, 10(1), S76–S83.

Ferreira, S. T., Vieira, M. N. N., & De Felice, F. G. (2007). Soluble protein oligomers as emerging toxins in Alzheimer's and other amyloid diseases. *IUBMB Life*, 59(4–5), 332–45.

Folch, J., Busquets, O., Ettcheto, M., Sánchez-López, E., Castro-Torres, R. D., Verdaguer, E., ... Camins, A. (2017). Memantine for the Treatment of

Dementia: A Review on its Current and Future Applications. *Journal of Alzheimer's Disease*, 1–18.

Friedland, R. P. (2003). Fish consumption and the risk of Alzheimer disease: is it time to make dietary recommendations? *Archives of Neurology*, 60(7), 923–4.

Fröjdö, S., Vidal, H., & Pirola, L. (2009). Alterations of insulin signaling in type 2 diabetes: a review of the current evidence from humans. *Biochimica et Biophysica Acta*, 1792(2), 83–92.

Fuentes, F., Zimmer, D., Atienza, M., Schottenfeld, J., Penkala, I., Bale, T., ... Arregui, C. O. (2012). Protein tyrosine phosphatase PTP1B is involved in hippocampal synapse formation and learning. *PLoS One*, 7(7), e41536.

G

Gamba, P., Testa, G., Sottero, B., Gargiulo, S., Poli, G., & Leonarduzzi, G. (2012). The link between altered cholesterol metabolism and Alzheimer's disease. *Annals of the New York Academy of Sciences*, 1259(1), 54–64.

Garcia-Alloza, M., Robbins, E. M., Zhang-Nunes, S. X., Purcell, S. M., Betensky, R. A., Raju, S., ... Frosch, M. P. (2006). Characterization of amyloid deposition in the APP^{swe}/PS1^{dE9} mouse model of Alzheimer disease. *Neurobiology of Disease*, 24(3), 516–524.

Gerzon, K., Krumkalns, E. V, Brindle, R. L., Marshall, F. J., & Root, M. A. (1963). The adamantyl group in medicinal agents. I. Hypoglycemic N-arylsulfonyl-N'-adamantylureas. *Journal of Medicinal Chemistry*, 6, 760–3.

Gibson, G. E., Sheu, K. F., Blass, J. P., Baker, A., Carlson, K. C., Harding, B., & Perrino, P. (1988). Reduced activities of thiamine-dependent enzymes in the brains and peripheral tissues of patients with Alzheimer's disease. *Archives of Neurology*, 45(8), 836–40.

Gispén, W. H., & Biessels, G. J. (2000). Cognition and synaptic plasticity in diabetes mellitus. *Trends in Neurosciences*, 23(11), 542–549.

Glass, C. K., Saijo, K., Winner, B., Marchetto, M. C., & Gage, F. H. (2010). Mechanisms Underlying Inflammation in Neurodegeneration. *Cell*, 140(6), 918–934.

Glénner, G. G., & Wong, C. W. (1984). Alzheimer's disease and Down's syndrome: Sharing of a unique cerebrovascular amyloid fibril protein. *Biochemical and Biophysical Research Communications*, 122(3), 1131–1135.

Gold, S. M., Dziobek, I., Sweat, V., Tirsi, A., Rogers, K., Bruehl, H., ... Convit, A. (2007). Hippocampal damage and memory impairments as possible early brain complications of type 2 diabetes. *Diabetologia*, 50(4), 711–719.

Goldstein, J. L., Basu, S. K., Brunschede, G. Y., & Brown, M. S. (1976). Release of low density lipoprotein from its cell surface receptor by sulfated glycosaminoglycans. *Cell*, 7(1), 85–95.

Goldstein, J. L., & Brown, M. S. (1974). Binding and degradation of low density lipoproteins by cultured human fibroblasts. Comparison of cells from a normal subject and from a patient with homozygous familial hypercholesterolemia. *The Journal of Biological Chemistry*, 249(16), 5153–62.

Gómez-Isla, T., Hollister, R., West, H., Mui, S., Growdon, J. H., Petersen, R. C., ... Hyman, B. T. (1997). Neuronal loss correlates with but exceeds neurofibrillary tangles in Alzheimer's disease. *Annals of Neurology*, *41*(1), 17–24.

Greenamyre, J. T., & Porter, R. H. (1994). Anatomy and physiology of glutamate in the CNS. *Neurology*, *44*(11 Suppl 8), S7-13.

Guimerà, A., Gironès, X., Cruz-Sánchez, F. F. (2002). Actualización sobre la Enfermedad de Alzheimer. *Revista Española de Patología*, *35*(1), 21–48

H

Haan, M. N. (2006). Therapy Insight: type 2 diabetes mellitus and the risk of late-onset Alzheimer's disease. *Nature Clinical Practice. Neurology*, *2*(3), 159–66.

Habbas, S., Santello, M., Becker, D., Stubbe, H., Zappia, G., Liaudet, N., ... Volterra, A. (2015). Neuroinflammatory TNF α Impairs Memory via Astrocyte Signaling. *Cell*, *163*(7), 1730–41.

Hall, A. M., & Roberson, E. D. (2012). Mouse models of Alzheimer's disease. *Brain Research Bulletin*, *88*(1), 3–12.

Han, W., & Li, C. (2010). Linking type 2 diabetes and Alzheimer's disease. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(15), 6557–8.

Handschin, C., & Spiegelman, B. M. (2006). Peroxisome Proliferator-Activated Receptor γ Coactivator 1 Coactivators, Energy Homeostasis, and Metabolism. *Endocrine Reviews*, 27(7), 728–735.

Hanisch, U. K., & Kettenmann, H. (2007). Microglia: active sensor and versatile effector cells in the normal and pathologic brain. *Nature Neuroscience*, 10(11), 1387–94.

Hardy, J., & Allsop, D. (1991). Amyloid deposition as the central event in the aetiology of Alzheimer's disease. *Trends in Pharmacological Sciences*, 12(10), 383–8.

Hardy, J. A., & Higgins, G. A. (1992). Alzheimer's disease: the amyloid cascade hypothesis. *Science (New York, N.Y.)*, 256(5054), 184–5.

Hardy, J., & Selkoe, D. J. (2002). The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science (New York, N.Y.)*, 297(5580), 353–6.

Havrankova, J., Roth, J., & Brownstein, M. J. (1979). Concentrations of insulin and insulin receptors in the brain are independent of peripheral insulin levels. Studies of obese and streptozotocin-treated rodents. *The Journal of Clinical Investigation*, 64(2), 636–42.

Hensley, K. (2010). Neuroinflammation in Alzheimer's disease: mechanisms, pathologic consequences, and potential for therapeutic manipulation. *Journal of Alzheimer's Disease*: 21(1), 1–14

Hernández, F., Gómez de Barreda, E., Fuster-Matanzo, A., Lucas, J. J., & Avila, J. (2010). GSK3: a possible link between beta amyloid peptide and tau protein. *Experimental Neurology*, 223(2), 322–5.

Hickman, S. E., Allison, E. K., & El Khoury, J. (2008). Microglial dysfunction and defective beta-amyloid clearance pathways in aging Alzheimer's disease mice. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 28(33), 8354–60.

Ho, L., Qin, W., Pompl, P. N., Xiang, Z., Wang, J., Zhao, Z., ... Pasinetti, G. M. (2004). Diet-induced insulin resistance promotes amyloidosis in a transgenic mouse model of Alzheimer's disease. *The FASEB Journal*, 18(7), 902–904.

Hokama, M., Oka, S., Leon, J., Ninomiya, T., Honda, H., Sasaki, K., ... Nakabeppu, Y. (2014). Altered Expression of Diabetes-Related Genes in Alzheimer's Disease Brains: The Hisayama Study. *Cerebral Cortex*, 24(9), 2476–2488.

Holtzman, D. M., Morris, J. C. and Goate, A. M. (2011) 'Alzheimer's disease: the challenge of the second century.', *Science translational medicine*, 3(77), p. 77sr1.

Hooper, C., Killick, R., & Lovestone, S. (2008). The GSK3 hypothesis of Alzheimer's disease. *Journal of Neurochemistry*, 104(6), 1433–9.

Hoozemans, J. J. M., Veerhuis, R., Rozemuller, J. M., & Eikelenboom, P. (2006). Neuroinflammation and regeneration in the early stages of Alzheimer's disease pathology. *International Journal of Developmental Neuroscience: The Official Journal of the International Society for Developmental Neuroscience*, 24(2–3), 157–165.

I

in t' Veld, B. A., Ruitenbergh, A., Hofman, A., Launer, L. J., van Duijn, C. M., Stijnen, T., ... Stricker, B. H. (2001). Nonsteroidal antiinflammatory drugs and the risk of Alzheimer's disease. *The New England Journal of Medicine*, 345(21), 1515–21

Inglis, F. (2002). The tolerability and safety of cholinesterase inhibitors in the treatment of dementia. *International Journal of Clinical Practice. Supplement*, (127), 45–63.

Innerarity, T. L., Pitas, R. E., & Mahley, R. W. (1986). Lipoprotein-receptor interactions. *Methods in Enzymology*, 129, 542–565.

Irvine, K., Laws, K. R., Gale, T. M., & Kondel, T. K. (2012). Greater cognitive deterioration in women than men with Alzheimer's disease: a meta analysis. *Journal of Clinical and Experimental Neuropsychology*, 34(9), 989–998.

Ito, K., Tatebe, T., Suzuki, K., Hirayama, T., Hayakawa, M., Kubo, H., ... Makino, M. (2017). Memantine reduces the production of amyloid- β peptides through modulation of amyloid precursor protein trafficking. *European Journal of Pharmacology*, 798, 16–25.

J

Jankowsky, J. L., Fadale, D. J., Anderson, J., Xu, G. M., Gonzales, V., Jenkins, N. A., ... Borchelt, D. R. (2004). Mutant presenilins specifically elevate the levels of the 42 residue beta-amyloid peptide in vivo: evidence for

augmentation of a 42-specific gamma secretase. *Human Molecular Genetics*, 13(2), 159–70.

Jarrett, J. T., Berger, E. P., & Lansbury, P. T. (1993). The C-terminus of the beta protein is critical in amyloidogenesis. *Annals of the New York Academy of Sciences*, 695, 144–8.

Jellinger, K. A. (2004). Head injury and dementia. *Current Opinion in Neurology*, 17(6), 719–23.

Jha, N. K., Jha, S. K., Kumar, D., Kejriwal, N., Sharma, R., Ambasta, R. K., & Kumar, P. (2015). Impact of Insulin Degrading Enzyme and Neprilysin in Alzheimer's Disease Biology: Characterization of Putative Cognates for Therapeutic Applications. *Journal of Alzheimer's Disease: JAD*, 48(4), 891–917.

Jin, M., Shepardson, N., Yang, T., Chen, G., Walsh, D., & Selkoe, D. J. (2011). Soluble amyloid beta-protein dimers isolated from Alzheimer cortex directly induce Tau hyperphosphorylation and neuritic degeneration. *Proceedings of the National Academy of Sciences of the United States of America*, 108(14), 5819–24.

Jing, Z., Caltagarone, J., & Bowser, R. (2009). Altered subcellular distribution of c-Abl in Alzheimer's disease. *Journal of Alzheimer's Disease: JAD*, 17(2), 409–22.

Joachim, C. L., Mori, H., & Selkoe, D. J. (1989). Amyloid β -protein deposition in tissues other than brain in Alzheimer's disease. *Nature*, 341(6239), 226–230.

Jope, R. S., Yuskaitis, C. J., & Beurel, E. (2007). Glycogen synthase kinase-3 (GSK3): inflammation, diseases, and therapeutics. *Neurochemical Research*, 32(4–5), 577–95.

Julien, C., Tremblay, C., Phivilay, A., Berthiaume, L., Emond, V., Julien, P., & Calon, F. (2010). High-fat diet aggravates amyloid-beta and tau pathologies in the 3xTg-AD mouse model. *Neurobiology of Aging*, 31(9), 1516–31.

K

Kaehler, S. T., Phleps, W., & Hesse, E. (2003). Dexibuprofen: pharmacology, therapeutic uses and safety. *Inflammopharmacology*, 11(4), 371–83.

Kalmijn, S., Launer, L. J., Ott, A., Witteman, J. C., Hofman, A., & Breteler, M. M. (1997). Dietary fat intake and the risk of incident dementia in the Rotterdam Study. *Annals of Neurology*, 42(5), 776–82.

Kandel, E. R. (2012). The molecular biology of memory: cAMP, PKA, CRE, CREB-1, CREB-2, and CPEB. *Molecular Brain*, 5(1), 14.

Katsouri, L., Parr, C., Bogdanovic, N., Willem, M., & Sastre, M. (2011). PPAR γ co-activator-1 α (PGC-1 α) reduces amyloid- β generation through a PPAR γ -dependent mechanism. *Journal of Alzheimer's Disease: JAD*, 25(1), 151–62.

Kew, J. N. C., & Kemp, J. A. (2005). Ionotropic and metabotropic glutamate receptor structure and pharmacology. *Psychopharmacology*, 179(1), 4–29.

Khachaturian, Z. S. (1985). Diagnosis of Alzheimer's disease. *Archives of Neurology*, 42(11), 1097–105.

Kim, T.-S., Pae, C.-U., Yoon, S.-J., Jang, W.-Y., Lee, N. J., Kim, J.-J., ... Lee, C.-U. (2006). Decreased plasma antioxidants in patients with Alzheimer's disease. *International Journal of Geriatric Psychiatry*, 21(4), 344–348.

Kimura, T., Hatsuta, H., Masuda-Suzukake, M., Hosokawa, M., Ishiguro, K., Akiyama, H., ... Hisanaga, S. (2016). The Abundance of Nonphosphorylated Tau in Mouse and Human Tauopathy Brains Revealed by the Use of Phos-Tag Method. *The American Journal of Pathology*, 186(2), 398–409.

Kish, S. J., Bergeron, C., Rajput, A., Dozic, S., Mastrogiacomo, F., Chang, L. J., ... Nobrega, J. N. (1992). Brain cytochrome oxidase in Alzheimer's disease. *Journal of Neurochemistry*, 59(2), 776–9.

Knight, E. M., Martins, I. V. A., Gümüşgöz, S., Allan, S. M., & Lawrence, C. B. (2014). High-fat diet-induced memory impairment in triple-transgenic Alzheimer's disease (3xTgAD) mice is independent of changes in amyloid and tau pathology. *Neurobiology of Aging*, 35(8), 1821–32.

Knutti, D., & Kralli, A. (2001). PGC-1, a versatile coactivator. *Trends in Endocrinology and Metabolism: TEM*, 12(8), 360–5.

Kowalska, A., Pruchnik-Wolińska, D., Florczak, J., Modestowicz, R., Szczech, J., Kozubski, W., ... Wender, M. (2004). Genetic study of familial cases of Alzheimer's disease. *Acta Biochimica Polonica*, 51(1), 245–252.

Kuhn, P.-H., Wang, H., Dislich, B., Colombo, A., Zeitschel, U., Ellwart, J. W., ... Lichtenthaler, S. F. (2010). ADAM10 is the physiologically relevant, constitutive alpha-secretase of the amyloid precursor protein in primary neurons. *The EMBO Journal*, 29(17), 3020–3032.

L

Laird, F. M., Cai, H., Savonenko, A. V., Farah, M. H., He, K., Melnikova, T., ... Wong, P. C. (2005). BACE1, a major determinant of selective vulnerability of the brain to amyloid-beta amyloidogenesis, is essential for cognitive, emotional, and synaptic functions. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 25(50), 11693–709.

Lawson, L. J., Perry, V. H., Dri, P., & Gordon, S. (1990). Heterogeneity in the distribution and morphology of microglia in the normal adult mouse brain. *Neuroscience*, 39(1), 151–70.

Leboucher, A., Laurent, C., Fernandez-Gomez, F.-J., Burnouf, S., Troquier, L., Eddarkaoui, S., ... Blum, D. (2013). Detrimental effects of diet-induced obesity on τ pathology are independent of insulin resistance in τ transgenic mice. *Diabetes*, 62(5), 1681–8.

Lechin, F., van der Dijs, B., Pardey-Maldonado, B., Rivera, J. E., Lechin, M. E., & Baez, S. (2009). Amantadine reduces glucagon and enhances insulin secretion throughout the oral glucose tolerance test: central plus peripheral nervous system mechanisms. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, 2, 203–13.

Lee, J., & Pilch, P. F. (1994). The insulin receptor: structure, function, and signaling. *The American Journal of Physiology*, 266(2 Pt 1), C319-34.

Lee, Y.-H., Tharp, W. G., Maple, R. L., Nair, S., Permana, P. A., & Pratley, R. E. (2008). Amyloid Precursor Protein Expression Is Upregulated in Adipocytes in Obesity. *Obesity*, 16(7), 1493

Leissring, M. A., Farris, W., Chang, A. Y., Walsh, D. M., Wu, X., Sun, X., ... Selkoe, D. J. (2003). Enhanced proteolysis of beta-amyloid in APP transgenic mice prevents plaque formation, secondary pathology, and premature death. *Neuron*, *40*(6), 1087–93.

Leuner, K., Hauptmann, S., Abdel-Kader, R., Scherping, I., Keil, U., Strosznajder, J. B., ... Müller, W. E. (2007). Mitochondrial dysfunction: the first domino in brain aging and Alzheimer's disease? *Antioxidants & Redox Signaling*, *9*(10), 1659–75.

Léveillé, F., El Gaamouch, F., Gouix, E., Lecocq, M., Lobner, D., Nicole, O., & Buisson, A. (2008). Neuronal viability is controlled by a functional relation between synaptic and extrasynaptic NMDA receptors. *FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology*, *22*(12), 4258–4271.

Lewczuk, P., Mroczko, B., Fagan, A., & Kornhuber, J. (2015). Biomarkers of Alzheimer's disease and mild cognitive impairment: a current perspective. *Advances in Medical Sciences*, *60*(1), 76–82.

Li, J., Zhao, W.-G., Shen, Z.-F., Yuan, T., Liu, S.-N., Liu, Q., ... Sun, W. (2015). Comparative Proteome Analysis of Brown Adipose Tissue in Obese C57BL/6J Mice Using iTRAQ-Coupled 2D LC-MS/MS. *PLOS ONE*, *10*(3), e0119350.

Li, Q. X., Fuller, S. J., Beyreuther, K., & Masters, C. L. (1999). The amyloid precursor protein of Alzheimer disease in human brain and blood. *Journal of Leukocyte Biology*, *66*(4), 567–74.

Li, Y., Rinne, J. O., Mosconi, L., Pirraglia, E., Rusinek, H., DeSanti, S., ... de Leon, M. J. (2008). Regional analysis of FDG and PIB-PET images in normal

aging, mild cognitive impairment, and Alzheimer's disease. *European Journal of Nuclear Medicine and Molecular Imaging*, 35(12), 2169–81.

Li, W., Poteet, E., Xie, L., Liu, R., Wen, Y., & Yang, S.-H. (2011). Regulation of matrix metalloproteinase 2 by oligomeric amyloid β protein. *Brain Research*, 1387, 141–8.

Lipton, S. A., Rosenberg, P. A., & Rosenberg, P. A. (1994). Excitatory amino acids as a final common pathway for neurologic disorders. *The New England Journal of Medicine*, 330(9), 613–22.

Liu, B., & Hong, J.-S. (2003). Role of microglia in inflammation-mediated neurodegenerative diseases: mechanisms and strategies for therapeutic intervention. *The Journal of Pharmacology and Experimental Therapeutics*, 304(1), 1–7.

Liu, C.-C., Hu, J., Tsai, C.-W., Yue, M., Melrose, H. L., Kanekiyo, T., & Bu, G. (2015). Neuronal LRP1 regulates glucose metabolism and insulin signaling in the brain. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 35(14), 5851–9.

Liu, Y., Zhang, Y.-W., Wang, X., Zhang, H., You, X., Liao, F.-F., & Xu, H. (2009). Intracellular trafficking of presenilin 1 is regulated by beta-amyloid precursor protein and phospholipase D1. *The Journal of Biological Chemistry*, 284(18), 12145–52.

Liu, Y., Liu, F., Grundke-Iqbal, I., Iqbal, K., & Gong, C.-X. (2011). Deficient brain insulin signalling pathway in Alzheimer's disease and diabetes. *The Journal of Pathology*, 225(1), 54–62.

Lowell, B. B., & Shulman, G. I. (2005). Mitochondrial Dysfunction and Type 2 Diabetes. *Science*, 307(5708), 384–387.

Luchsinger, J. A., Tang, M.-X., Shea, S., & Mayeux, R. (2002). Caloric intake and the risk of Alzheimer disease. *Archives of Neurology*, 59(8), 1258–63.

Luchsinger, J. A., Reitz, C., Honig, L. S., Tang, M. X., Shea, S., & Mayeux, R. (2005). Aggregation of vascular risk factors and risk of incident Alzheimer disease. *Neurology*, 65(4), 545–551.

Lye, T. C., & Shores, E. A. (2000). Traumatic brain injury as a risk factor for Alzheimer's disease: a review. *Neuropsychology Review*, 10(2), 115–129.

M

Maccioni, R. B., Muñoz, J. P., & Barbeito, L. (2001). The molecular bases of Alzheimer's disease and other neurodegenerative disorders. *Archives of Medical Research*, 32(5), 367–81.

Mackenzie, I. R., & Munoz, D. G. (1998). Nonsteroidal anti-inflammatory drug use and Alzheimer-type pathology in aging. *Neurology*, 50(4), 986–90.

Macklin, L., Griffith, C. M., Cai, Y., Rose, G. M., Yan, X.-X., & Patrylo, P. R. (2017). Glucose tolerance and insulin sensitivity are impaired in APP/PS1 transgenic mice prior to amyloid plaque pathogenesis and cognitive decline. *Experimental Gerontology*, 88, 9–18.

Maesako, M., Uemura, K., Iwata, A., Kubota, M., Watanabe, K., Uemura, M., ... Kinoshita, A. (2013). Continuation of exercise is necessary to inhibit high

fat diet-induced β -amyloid deposition and memory deficit in amyloid precursor protein transgenic mice. *PLoS One*, 8(9), e72796.

Mahley, R. (1988). Apolipoprotein E: cholesterol transport protein with expanding role in cell biology. *Science*, 240(4852), 622–630.

Marquard, J., Otter, S., Welters, A., Stirban, A., Fischer, A., Eglinger, J., ...

Lammert, E. (2015). Characterization of pancreatic NMDA receptors as possible drug targets for diabetes treatment. *Nature Medicine*, 21(4), 363–72.

Marsa, L. (2015) Cracking the Alzheimer's Code; Are we close to conquering one of the most puzzling disease of our time? *Science for the curious discover*. Recuperado de: <http://discovermagazine.com/2015/march/16-cracking-the-alzheimers-code>

Masliah, E., Mallory, M., Alford, M., DeTeresa, R., Hansen, L. A., McKeel, D. W., & Morris, J. C. (2001). Altered expression of synaptic proteins occurs early during progression of Alzheimer's disease. *Neurology*, 56(1), 127–9.

Mao, Y.-F., Guo, Z., Zheng, T., Jiang, Y., Yan, Y., Yin, X., ... Zhang, B. (2016). Intranasal insulin alleviates cognitive deficits and amyloid pathology in young adult APP^{swe}/PS1^{dE9} mice. *Aging Cell*, 15(5), 893–902.

Maragakis, N. J., & Rothstein, J. D. (2006). Mechanisms of Disease: astrocytes in neurodegenerative disease. *Nature Clinical Practice. Neurology*, 2(12), 679–89.

Markesbery, W. R. (1997). Oxidative stress hypothesis in Alzheimer's disease. *Free Radical Biology & Medicine*, 23(1), 134–47.

Markesbery, W. R., & Carney, J. M. (1999). Oxidative alterations in Alzheimer's disease. *Brain Pathology (Zurich, Switzerland)*, 9(1), 133–46.

Margolis, R. U., & Altszuler, N. (1967). Insulin in the cerebrospinal fluid. *Nature*, 215(5108), 1375–6.

Martinez, A., Castro, A., Dorransoro, I., & Alonso, M. (2002). Glycogen synthase kinase 3 (GSK-3) inhibitors as new promising drugs for diabetes, neurodegeneration, cancer, and inflammation. *Medicinal Research Reviews*, 22(4), 373–84.

Masters, C. L., & Beyreuther, K. (2006). Alzheimer's centennial legacy: prospects for rational therapeutic intervention targeting the Abeta amyloid pathway. *Brain: A Journal of Neurology*, 129(Pt 11), 2823–39.

Mattson, M. P. (2000). Neuroprotective signaling and the aging brain: take away my food and let me run. *Brain Research*, 886(1–2), 47–53.

Mattson, M. P. (2004). Pathways towards and away from Alzheimer's disease. *Nature*, 430(7000), 631–639.

Mawuenyega, K. G., Sigurdson, W., Ovod, V., Munsell, L., Kasten, T., Morris, J. C., ... Bateman, R. J. (2010). Decreased Clearance of CNS β -Amyloid in Alzheimer's Disease. *Science*, 330(6012), 1774–1774.

Maynard, C. J. *et al.* (2006) 'Gender and genetic background effects on brain metal levels in APP transgenic and normal mice: implications for Alzheimer beta-amyloid pathology.', *Journal of inorganic biochemistry*, 100(5–6), pp. 952–62

McCrimmon, R. J., Ryan, C. M., & Frier, B. M. (2012). Diabetes and cognitive dysfunction. *Lancet (London, England)*, 379(9833), 2291–9.

McGeer, E. G., & McGeer, P. L. (2010). Neuroinflammation in Alzheimer's disease and mild cognitive impairment: a field in its infancy. *Journal of Alzheimer's Disease : JAD*, 19(1), 355–61

McGeer, P. L., Schulzer, M., & McGeer, E. G. (1996). Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease: a review of 17 epidemiologic studies. *Neurology*, 47(2), 425–32.

Mejía-Arango, S., & Zúñiga-Gil, C. (2011). [Diabetes mellitus as a risk factor for dementia in the Mexican elder population]. *Revista de Neurología*, 53(7), 397–405.

Mesulam, M. (2004). The cholinergic lesion of Alzheimer's disease: pivotal factor or side show? *Learning & Memory (Cold Spring Harbor, N.Y.)*, 11(1), 43–9.

Miners, J. S., Van Helmond, Z., Chalmers, K., Wilcock, G., Love, S., & Kehoe, P. G. (2006). Decreased expression and activity of neprilysin in Alzheimer disease are associated with cerebral amyloid angiopathy. *Journal of Neuropathology and Experimental Neurology*, 65(10), 1012–21.

Mohs, R. C., Doody, R. S., Morris, J. C., Ieni, J. R., Rogers, S. L., Perdomo, C. A., ... "312" Study Group. (2001). A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients. *Neurology*, 57(3), 481–8.

Molteni, R., Barnard, R. J., Ying, Z., Roberts, C. K., & Gómez-Pinilla, F. (2002). A high-fat, refined sugar diet reduces hippocampal brain-derived

neurotrophic factor, neuronal plasticity, and learning. *Neuroscience*, 112(4), 803–14.

Moreira, E. L. G., de Oliveira, J., Nunes, J. C., Santos, D. B., Nunes, F. C., Vieira, D. S. C., ... Prediger, R. D. (2012). Age-related cognitive decline in hypercholesterolemic LDL receptor knockout mice (LDLr^{-/-}): evidence of antioxidant imbalance and increased acetylcholinesterase activity in the prefrontal cortex. *Journal of Alzheimer's Disease: JAD*, 32(2), 495–511.

Moreira, P. I., Santos, M. S., & Oliveira, C. R. (2007). Alzheimer's disease: a lesson from mitochondrial dysfunction. *Antioxidants & Redox Signaling*, 9(10), 1621–30.

Morgen, K., & Frölich, L. (2015). The metabolism hypothesis of Alzheimer's disease: from the concept of central insulin resistance and associated consequences to insulin therapy. *Journal of Neural Transmission (Vienna, Austria: 1996)*, 122(4), 499–504.

Mori, T., Koyama, N., Segawa, T., Maeda, M., Maruyama, N., Kinoshita, N., ... Town, T. (2014). Methylene blue modulates β -secretase, reverses cerebral amyloidosis, and improves cognition in transgenic mice. *The Journal of Biological Chemistry*, 289(44), 30303–17.

Morris, G. P., Clark, I. A. and Vissel, B. (2014) 'Inconsistencies and controversies surrounding the amyloid hypothesis of Alzheimer's disease.', *Acta neuropathologica communications*, 2(1), p. 135.

Morris, M. C., Evans, D. A., Bienias, J. L., Tangney, C. C., Bennett, D. A., Aggarwal, N., ... Wilson, R. S. (2003). Dietary fats and the risk of incident Alzheimer disease. *Archives of Neurology*, 60(2), 194–200.

Morris, J. K., Honea, R. A., Vidoni, E. D., Swerdlow, R. H., & Burns, J. M. (2014). Is Alzheimer's disease a systemic disease? *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, 1842(9), 1340–1349.

N

Nazareth, A. M. de. (2017). Type 2 diabetes mellitus in the pathophysiology of Alzheimer's disease. *Dementia & Neuropsychologia*, 11(2), 105–113.

Ni, R., Marutle, A., & Nordberg, A. (2013). Modulation of $\alpha 7$ nicotinic acetylcholine receptor and fibrillar amyloid- β interactions in Alzheimer's disease brain. *Journal of Alzheimer's Disease : JAD*, 33(3), 841–51.

Nitsch, R. M., Slack, B. E., Wurtman, R. J., & Growdon, J. H. (1992). Release of Alzheimer amyloid precursor derivatives stimulated by activation of muscarinic acetylcholine receptors. *Science (New York, N.Y.)*, 258(5080), 304–307.

Nunomura, A., Perry, G., Aliev, G., Hirai, K., Takeda, A., Balraj, E. K., ... Smith, M. A. (2001). Oxidative damage is the earliest event in Alzheimer disease. *Journal of Neuropathology and Experimental Neurology*, 60(8), 759–67.

Nuzzo, D., Picone, P., Baldassano, S., Caruana, L., Messina, E., Marino Gammazza, A., ... Di Carlo, M. (2015). Insulin Resistance as Common Molecular Denominator Linking Obesity to Alzheimer's Disease. *Current Alzheimer Research*, 12(8), 723–35.

O

Obici, S., Zhang, B. B., Karkanas, G., & Rossetti, L. (2002). Hypothalamic insulin signaling is required for inhibition of glucose production. *Nature Medicine*, 8(12), 1376–1382.

Oksman, M., Iivonen, H., Högges, E., Amtul, Z., Penke, B., Leenders, I., ... Tanila, H. (2006). Impact of different saturated fatty acid, polyunsaturated fatty acid and cholesterol containing diets on beta-amyloid accumulation in APP/PS1 transgenic mice. *Neurobiology of Disease*, 23(3), 563–72.

Olin, J., & Schneider, L. (2002). Galantamine for Alzheimer's disease. *The Cochrane Database of Systematic Reviews*, (3), CD001747.

Olney, J. W., Wozniak, D. F., & Farber, N. B. (1997). Excitotoxic neurodegeneration in Alzheimer disease. New hypothesis and new therapeutic strategies. *Archives of Neurology*, 54(10), 1234–40.

OMS (Organización Mundial de la Salud) (2017). Demencia. Recuperado febrero, 4, 2018 de <http://www.who.int/mediacentre/factsheets/fs362/es/>

OMS (Organización Mundial de la Salud) (2017). Diabetes. Recuperado febrero 4, 2018 de <http://www.who.int/mediacentre/factsheets/fs312/es/>

P

Pan, M.-H., Lai, C.-S., & Ho, C.-T. (2010). Anti-inflammatory activity of natural dietary flavonoids. *Food & Function*, 1(1), 15–31.

Paoletti, P., Bellone, C., & Zhou, Q. (2013). NMDA receptor subunit diversity: impact on receptor properties, synaptic plasticity and disease. *Nature Reviews. Neuroscience*, *14*(6), 383–400.

Paradies, G., Petrosillo, G., Paradies, V., & Ruggiero, F. M. (2011). Mitochondrial dysfunction in brain aging: Role of oxidative stress and cardiolipin. *Neurochemistry International*, *58*(4), 447–457.

Pasinetti, G. M., Zhao, Z., Qin, W., Ho, L., Shrishailam, Y., Macgrogan, D., ... Wang, J. (2007). Caloric intake and Alzheimer's disease. Experimental approaches and therapeutic implications. *Interdisciplinary Topics in Gerontology*, *35*, 159–75.

Patzke, H., Maddineni, U., Ayala, R., Morabito, M., Volker, J., Dikkes, P., ... Tsai, L.-H. (2003). Partial rescue of the p35^{-/-} brain phenotype by low expression of a neuronal-specific enolase p25 transgene. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *23*(7), 2769–78.

Pedrós, I., Petrov, D., Allgaier, M., Sureda, F., Barroso, E., Beas-Zarate, C., ... Camins, A. (2014). Early alterations in energy metabolism in the hippocampus of APP^{swe}/PS1^{dE9} mouse model of Alzheimer's disease. *Biochimica et Biophysica Acta*, *1842*(9), 1556–66.

Peila, R., Rodriguez, B. L., & Launer, L. J. (2002). Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: The Honolulu-Asia Aging Study. *Diabetes*, *51*(4), 1256–62.

Perry, G., Nunomura, A., Hirai, K., Zhu, X., Pérez, M., Avila, J., ... Smith, M. A. (2002). Is oxidative damage the fundamental pathogenic mechanism of

- Alzheimer's and other neurodegenerative diseases? *Free Radical Biology & Medicine*, 33(11), 1475–9.
- Piaceri, I., Nacmias, B. and Sorbi, S. (2013) 'Genetics of familial and sporadic Alzheimer's disease.', *Frontiers in bioscience (Elite edition)*, 5, pp. 167–77.
- Pimplikar, S. W., Nixon, R. A., Robakis, N. K., Shen, J., & Tsai, L.-H. (2010). Amyloid-Independent Mechanisms in Alzheimer's Disease Pathogenesis. *Journal of Neuroscience*, 30(45), 14946–14954.
- Pittel, Z., Heldman, E., Barg, J., Haring, R., & Fisher, A. (1996). Muscarinic control of amyloid precursor protein secretion in rat cerebral cortex and cerebellum. *Brain Research*, 742(1–2), 299–304.
- Plum, L., Schubert, M., & Brüning, J. C. (2005). The role of insulin receptor signaling in the brain. *Trends in Endocrinology & Metabolism*, 16(2), 59–65.
- Poirier, J. (2000). Apolipoprotein E and Alzheimer's disease. A role in amyloid catabolism. *Annals of the New York Academy of Sciences*, 924, 81–90.
- Postina, R., Schroeder, A., Dewachter, I., Bohl, J., Schmitt, U., Kojro, E., ... Fahrenholz, F. (2004). A disintegrin-metalloproteinase prevents amyloid plaque formation and hippocampal defects in an Alzheimer disease mouse model. *The Journal of Clinical Investigation*, 113(10), 1456–64.
- Profenno, L. A., Porsteinsson, A. P., & Faraone, S. V. (2010). Meta-analysis of Alzheimer's disease risk with obesity, diabetes, and related disorders. *Biological Psychiatry*, 67(6), 505–12.
- Puig, K. L., Floden, A. M., Adhikari, R., Golovko, M. Y., & Combs, C. K. (2012). Amyloid precursor protein and proinflammatory changes are regulated

in brain and adipose tissue in a murine model of high fat diet-induced obesity. *PloS One*, 7(1), e30378.

Puigserver, P., & Spiegelman, B. M. (2003). Peroxisome Proliferator-Activated Receptor- γ Coactivator 1 α (PGC-1 α): Transcriptional Coactivator and Metabolic Regulator. *Endocrine Reviews*, 24(1), 78–90.

Pujadas, L., Rossi, D., Andrés, R., Teixeira, C. M., Serra-Vidal, B., Parcerisas, A., ... Soriano, E. (2014). Reelin delays amyloid-beta fibril formation and rescues cognitive deficits in a model of Alzheimer's disease. *Nature Communications*, 5, 3443.

Q

Qin, W., Haroutunian, V., Katsel, P., Cardozo, C. P., Ho, L., Buxbaum, J. D., & Pasinetti, G. M. (2009). PGC-1 α Expression Decreases in the Alzheimer Disease Brain as a Function of Dementia. *Archives of Neurology*, 66(3), 352–61.

Qin, W., Zhao, W., Ho, L., Wang, J., Walsh, K., Gandy, S., & Pasinetti, G. M. (2008). Regulation of forkhead transcription factor FoxO3a contributes to calorie restriction-induced prevention of Alzheimer's disease-type amyloid neuropathology and spatial memory deterioration. *Annals of the New York Academy of Sciences*, 1147(1), 335–47.

Qiu, W. Q., & Folstein, M. F. (2006). Insulin, insulin-degrading enzyme and amyloid-beta peptide in Alzheimer's disease: review and hypothesis. *Neurobiology of Aging*, 27(2), 190–8.

R

Rafalski, V. A., Ho, P. P., Brett, J. O., Ucar, D., Dugas, J. C., Pollina, E. A., ... Brunet, A. (2013). Expansion of oligodendrocyte progenitor cells following SIRT1 inactivation in the adult brain. *Nature Cell Biology*, *15*(6), 614–24.

Rajasekar, N., Nath, C., Hanif, K., & Shukla, R. (2016). Inhibitory Effect of Memantine on Streptozotocin-Induced Insulin Receptor Dysfunction, Neuroinflammation, Amyloidogenesis, and Neurotrophic Factor Decline in Astrocytes. *Molecular Neurobiology*, *53*(10), 6730–6744.

Ramos-Rodriguez, J. J., Ortiz-Barajas, O., Gamero-Carrasco, C., de la Rosa, P. R., Infante-Garcia, C., Zopeque-Garcia, N., ... Garcia-Alloza, M. (2014). Prediabetes-induced vascular alterations exacerbate central pathology in APP^{swe}/PS1^{dE9} mice. *Psychoneuroendocrinology*, *48*, 123–35.

Ramos-Rodriguez, J. J., Spires-Jones, T., Pooler, A. M., Lechuga-Sancho, A. M., Bacskai, B. J., & Garcia-Alloza, M. (2017). Progressive Neuronal Pathology and Synaptic Loss Induced by Prediabetes and Type 2 Diabetes in a Mouse Model of Alzheimer's Disease. *Molecular Neurobiology*, *54*(5), 3428–3438.

Reddy, P. H., & Beal, M. F. (2008). Amyloid beta, mitochondrial dysfunction and synaptic damage: implications for cognitive decline in aging and Alzheimer's disease. *Trends in Molecular Medicine*, *14*(2), 45–53.

Reed, B., Villeneuve, S., Mack, W., DeCarli, C., Chui, H. C., & Jagust, W. (2014). Associations between serum cholesterol levels and cerebral amyloidosis. *JAMA Neurology*, *71*(2), 195–200.

Refolo, L. M., Malester, B., LaFrancois, J., Bryant-Thomas, T., Wang, R., Tint, G. S., ... Pappolla, M. A. (2000). Hypercholesterolemia accelerates the Alzheimer's amyloid pathology in a transgenic mouse model. *Neurobiology of Disease*, 7(4), 321–31.

Reger, M. A., Watson, G. S., Frey, W. H., Baker, L. D., Cholerton, B., Keeling, M. L., ... Craft, S. (2006). Effects of intranasal insulin on cognition in memory-impaired older adults: Modulation by APOE genotype. *Neurobiology of Aging*, 27(3), 451–458.

Reger, M. A., Watson, G. S., Green, P. S., Baker, L. D., Cholerton, B., Fishel, M. A., ... Craft, S. (2008). Intranasal insulin administration dose-dependently modulates verbal memory and plasma amyloid-beta in memory-impaired older adults. *Journal of Alzheimer's Disease: JAD*, 13(3), 323–31.

Reiman, E. M., Caselli, R. J., Yun, L. S., Chen, K., Bandy, D., Minoshima, S., ... Osborne, D. (1996). Preclinical Evidence of Alzheimer's Disease in Persons Homozygous for the $\epsilon 4$ Allele for Apolipoprotein E. *New England Journal of Medicine*, 334(12), 752–758.

Reiman, E. M., Chen, K., Alexander, G. E., Caselli, R. J., Bandy, D., Osborne, D., ... Hardy, J. (2005). Correlations between apolipoprotein E epsilon4 gene dose and brain-imaging measurements of regional hypometabolism. *Proceedings of the National Academy of Sciences of the United States of America*, 102(23), 8299–302.

Reisberg, B., Doody, R., Stöffler, A., Schmitt, F., Ferris, S., Möbius, H. J., & Memantine Study Group. (2003). Memantine in moderate-to-severe Alzheimer's disease. *The New England Journal of Medicine*, 348(14), 1333–41.

Riedel, G., Platt, B., & Micheau, J. (2003). Glutamate receptor function in learning and memory. *Behavioural Brain Research*, *140*(1–2), 1–47.

Rigacci, S., Guidotti, V., Bucciantini, M., Nichino, D., Relini, A., Berti, A., & Stefani, M. (2011). A β (1-42) aggregates into non-toxic amyloid assemblies in the presence of the natural polyphenol oleuropein aglycon. *Current Alzheimer Research*, *8*(8), 841–52.

Ritchie, D. L., Adlard, P., Peden, A. H., Lowrie, S., Le Grice, M., Burns, K., ... Ironside, J. W. (2017). Amyloid- β accumulation in the CNS in human growth hormone recipients in the UK. *Acta Neuropathologica*, *134*(2), 221–240.

Roberson, E. D., Scarce-Levie, K., Palop, J. J., Yan, F., Cheng, I. H., Wu, T., ... Mucke, L. (2007). Reducing endogenous tau ameliorates amyloid beta-induced deficits in an Alzheimer's disease mouse model. *Science (New York, N.Y.)*, *316*(5825), 750–4.

Roberts, K. F., Elbert, D. L., Kasten, T. P., Patterson, B. W., Sigurdson, W. C., Connors, R. E., ... Bateman, R. J. (2014). Amyloid- β efflux from the central nervous system into the plasma. *Annals of Neurology*, *76*(6), 837–44.

Rocchi, A., Orsucci, D., Tognoni, G., Ceravolo, R., & Siciliano, G. (2009). The role of vascular factors in late-onset sporadic Alzheimer's disease. Genetic and molecular aspects. *Current Alzheimer Research*, *6*(3), 224–237.

Rogawski, M. A., & Wenk, G. L. (2003). The neuropharmacological basis for the use of memantine in the treatment of Alzheimer's disease. *CNS Drug Reviews*, *9*(3), 275–308.

- Roher, A. E., Kuo, Y. M., Kokjohn, K. M., Emmerling, M. R., & Gracon, S. (1999). Amyloid and lipids in the pathology of Alzheimer disease. *Amyloid: The International Journal of Experimental and Clinical Investigation: The Official Journal of the International Society of Amyloidosis*, 6(2), 136–45.
- Roher, A. E., Esh, C. L., Kokjohn, T. A., Castaño, E. M., Van Vickle, G. D., Kalback, W. M., ... Sabbagh, M. N. (2009). Amyloid beta peptides in human plasma and tissues and their significance for Alzheimer's disease. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, 5(1), 18–29.
- Rojo, L. E., Fernández, J. A., Maccioni, A. A., Jimenez, J. M., & Maccioni, R. B. (2008). Neuroinflammation: implications for the pathogenesis and molecular diagnosis of Alzheimer's disease. *Archives of Medical Research*, 39(1), 1–16.
- Román, G. C. (2003) 'Stroke, cognitive decline and vascular dementia: the silent epidemic of the 21st century.', *Neuroepidemiology*, 22(3), pp. 161–4.
- Rossner, S., Lange-Dohna, C., Zeitschel, U., & Perez-Polo, J. R. (2005). Alzheimer's disease beta-secretase BACE1 is not a neuron-specific enzyme. *Journal of Neurochemistry*, 92(2), 226–234.
- Rowland, K. C., Irby, N. K., & Spirou, G. A. (2000). Specialized synapse-associated structures within the calyx of Held. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 20(24), 9135–44.
- Ruan, L., Kang, Z., Pei, G., & Le, Y. (2009). Amyloid deposition and inflammation in APP^{swe}/PS1^{dE9} mouse model of Alzheimer's disease. *Current Alzheimer Research*, 6(6), 531–40.

Rush, T., & Buisson, A. (2014). Reciprocal disruption of neuronal signaling and A β production mediated by extrasynaptic NMDA receptors: a downward spiral. *Cell and Tissue Research*, 356(2), 279–286.

Rusinek, H., Ha, J., Yau, P. L., Storey, P., Tirsi, A., Tsui, W. H., ... Convit, A. (2015). Cerebral perfusion in insulin resistance and type 2 diabetes. *Journal of Cerebral Blood Flow and Metabolism : Official Journal of the International Society of Cerebral Blood Flow and Metabolism*, 35(1), 95–102.

S

Sagare, A. P., Bell, R. D., & Zlokovic, B. V. (2012). Neurovascular dysfunction and faulty amyloid β -peptide clearance in Alzheimer disease. *Cold Spring Harbor Perspectives in Medicine*, 2(10), a011452–a011452.

Sánchez-López, E., Ettcheto, M., Egea, M. A., Espina, M., Calpena, A. C., Folch, J., ... García, M. L. (2017). New potential strategies for Alzheimer's disease prevention: pegylated biodegradable dexibuprofen nanospheres administration to APP^{swe}/PS1^{dE9}. *Nanomedicine: Nanotechnology, Biology and Medicine*, 13(3), 1171–1182.

Santacruz, K., Lewis, J., Spire, T., Paulson, J., Kotilinek, L., Ingelsson, M., ... Ashe, K. H. (2005). Tau suppression in a neurodegenerative mouse model improves memory function. *Science (New York, N.Y.)*, 309(5733), 476–81.

Schlatterer, S. D., Acker, C. M., & Davies, P. (2011). c-Abl in Neurodegenerative Disease. *Journal of Molecular Neuroscience*, 45(3), 445–452.

Schneider, L. S., Mangialasche, F., Andreasen, N., Feldman, H., Giacobini, E., Jones, R., ... Kivipelto, M. (2014). Clinical trials and late-stage drug development for Alzheimer's disease: an appraisal from 1984 to 2014. *Journal of Internal Medicine*, 275(3), 251–283.

Schraen-Maschke, S., Sergeant, N., Dhaenens, C.-M., Bombois, S., Deramecourt, V., Caillet-Boudin, M.-L., ... Buée, L. (2008). Tau as a biomarker of neurodegenerative diseases. *Biomarkers in Medicine*, 2(4), 363–84.

Schwartz, M., Butovsky, O., Brück, W., & Hanisch, U.-K. (2006). Microglial phenotype: is the commitment reversible? *Trends in Neurosciences*, 29(2), 68–74.

Schwartz, M. W., Figlewicz, D. P., Baskin, D. G., Woods, S. C., & Porte, D. (1992). Insulin in the brain: a hormonal regulator of energy balance. *Endocrine Reviews*, 13(3), 387–414.

Segovia, G., Porrás, A., Del Arco, A., & Mora, F. (2001). Glutamatergic neurotransmission in aging: a critical perspective. *Mechanisms of Ageing and Development*, 122(1), 1–29.

Selkoe, D. J. (2002). Alzheimer's disease is a synaptic failure. *Science (New York, N.Y.)*, 298(5594), 789–91.

Selkoe, D. J. (2011) 'Alzheimer's Disease', *Cold Spring Harbor Perspectives in Biology*, 3(7), pp. a004457–a004457. doi: 10.1101/cshperspect.a004457.

Selkoe, D. J., & Hardy, J. (2016). The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Molecular Medicine*, 8(6), 595–608.

Sergeant, N., Delacourte, A., & Buée, L. (2005). Tau protein as a differential biomarker of tauopathies. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, 1739(2–3), 179–197.

Small, D. H. and Cappai, R. (2006) ‘Alois Alzheimer and Alzheimer’s disease: a centennial perspective.’, *Journal of neurochemistry*, 99(3), pp. 708–10.

Smith, E., Hay, P., Campbell, L., & Trollor, J. N. (2011). A review of the association between obesity and cognitive function across the lifespan: implications for novel approaches to prevention and treatment. *Obesity Reviews*, 12(9), 740–755.

Small, G. W., Mazziotta, J. C., Collins, M. T., Baxter, L. R., Phelps, M. E., Mandelkern, M. A., ... Chang, L. (1995). Apolipoprotein E type 4 allele and cerebral glucose metabolism in relatives at risk for familial Alzheimer disease. *JAMA*, 273(12), 942–7.

Snyder, E. M., Nong, Y., Almeida, C. G., Paul, S., Moran, T., Choi, E. Y., ... Greengard, P. (2005). Regulation of NMDA receptor trafficking by amyloid-beta. *Nature Neuroscience*, 8(8), 1051–8.

Solomon, A., Kåreholt, I., Ngandu, T., Winblad, B., Nissinen, A., Tuomilehto, J., ... Kivipelto, M. (2007). Serum cholesterol changes after midlife and late-life cognition: twenty-one-year follow-up study. *Neurology*, 68(10), 751–6.

Sommer, G., Kralisch, S., Lipfert, J., Weise, S., Krause, K., Jessnitzer, B., ... Fasshauer, M. (2009). Amyloid precursor protein expression is induced by tumor necrosis factor alpha in 3T3-L1 adipocytes. *Journal of Cellular Biochemistry*, 108(6), 1418–22.

Sorbi, S., Bird, E. D., & Blass, J. P. (1983). Decreased pyruvate dehydrogenase complex activity in Huntington and Alzheimer brain. *Annals of Neurology*, 13(1), 72–78.

Spencer, J. P. E., Vafeiadou, K., Williams, R. J., & Vauzour, D. (2012). Neuroinflammation: Modulation by flavonoids and mechanisms of action. *Molecular Aspects of Medicine*, 33(1), 83–97.

Steen, E., Terry, B. M., Rivera, E. J., Cannon, J. L., Neely, T. R., Tavares, R., ... de la Monte, S. M. (2005). Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease--is this type 3 diabetes? *Journal of Alzheimer's Disease : JAD*, 7(1), 63–80.

Stewart, W. F., Kawas, C., Corrada, M., & Metter, E. J. (1997). Risk of Alzheimer's disease and duration of NSAID use. *Neurology*, 48(3), 626–32.

Strachan, M. W., Deary, I. J., Ewing, F. M., & Frier, B. M. (1997). Is type II diabetes associated with an increased risk of cognitive dysfunction? A critical review of published studies. *Diabetes Care*, 20(3), 438–445.

Streit, W. J. (2002). Microglia as neuroprotective, immunocompetent cells of the CNS. *Glia*, 40(2), 133–9.

Strittmatter, W. J., & Roses, A. D. (1996). Apolipoprotein E and Alzheimer's Disease. *Annual Review of Neuroscience*, 19(1), 53–77.

Strittmatter, W. J., Saunders, A. M., Schmechel, D., Pericak-Vance, M., Enghild, J., Salvesen, G. S., & Roses, A. D. (1993). Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proceedings of the National Academy of Sciences of the United States of America*, 90(5), 1977–81.

Sui, H., Zhang, L., Liu, Z., & Jin, Y. (2015). Atorvastatin prevents A β oligomer-induced neurotoxicity in cultured rat hippocampal neurons by inhibiting Tau cleavage. *Acta Pharmacologica Sinica*, 36(5), 553–64.

Suzuki, M., Nelson, A. D., Eickstaedt, J. B., Wallace, K., Wright, L. S., & Svendsen, C. N. (2006). Glutamate enhances proliferation and neurogenesis in human neural progenitor cell cultures derived from the fetal cortex. *The European Journal of Neuroscience*, 24(3), 645–653.

Swerdlow, R. H., Burns, J. M., & Khan, S. M. (2010). The Alzheimer's Disease Mitochondrial Cascade Hypothesis. *Journal of Alzheimer's Disease*, 20(s2), S265–S279. <http://doi.org/10.3233/JAD-2010-100339>

Swerdlow, R. H., & Khan, S. M. (2004). A “mitochondrial cascade hypothesis” for sporadic Alzheimer's disease. *Medical Hypotheses*, 63(1), 8–20.

Swerdlow, R. H., Burns, J. M., & Khan, S. M. (2014). The Alzheimer's disease mitochondrial cascade hypothesis: Progress and perspectives. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, 1842(8), 1219–1231.

Szabados, T., Dul, C., Majtényi, K., Hargitai, J., Péntzes, Z., & Urbanics, R. (2004). A chronic Alzheimer's model evoked by mitochondrial poison sodium azide for pharmacological investigations. *Behavioural Brain Research*, 154(1), 31–40. <http://doi.org/10.1016/j.bbr.2004.01.016>

T

Tabet, N. (2006). Acetylcholinesterase inhibitors for Alzheimer's disease: anti-inflammatories in acetylcholine clothing! *Age and Ageing*, 35(4), 336–338.

Tabner, B. J., El-Agnaf, O. M. A., Turnbull, S., German, M. J., Paleologou, K. E., Hayashi, Y., ... Allsop, D. (2005). Hydrogen Peroxide Is Generated during the Very Early Stages of Aggregation of the Amyloid Peptides Implicated in Alzheimer Disease and Familial British Dementia. *Journal of Biological Chemistry*, 280(43), 35789–35792.

Takalo, M., Haapasalo, A., Martiskainen, H., Kurkinen, K. M. A., Koivisto, H., Miettinen, P., ... Hiltunen, M. (2014). High-fat diet increases tau expression in the brain of T2DM and AD mice independently of peripheral metabolic status. *The Journal of Nutritional Biochemistry*, 25(6), 634–41.

Takeda, S., Sato, N., Rakugi, H., & Morishita, R. (2011). Molecular mechanisms linking diabetes mellitus and Alzheimer disease: beta-amyloid peptide, insulin signaling, and neuronal function. *Molecular BioSystems*, 7(6), 1822.

Tamaki, C., Ohtsuki, S., Iwatsubo, T., Hashimoto, T., Yamada, K., Yabuki, C., & Terasaki, T. (2006). Major involvement of low-density lipoprotein receptor-related protein 1 in the clearance of plasma free amyloid beta-peptide by the liver. *Pharmaceutical Research*, 23(7), 1407–16.

Tang, B. L. (2009). Neuronal protein trafficking associated with Alzheimer disease: from APP and BACE1 to glutamate receptors. *Cell Adhesion & Migration*, 3(1), 118–28.

Tanti, J.-F., & Jager, J. (2009). Cellular mechanisms of insulin resistance: role of stress-regulated serine kinases and insulin receptor substrates (IRS) serine phosphorylation. *Current Opinion in Pharmacology*, 9(6), 753–62.

Tarasoff-Conway, J. M., Carare, R. O., Osorio, R. S., Glodzik, L., Butler, T., Fieremans, E., ... de Leon, M. J. (2015). Clearance systems in the brain—implications for Alzheimer disease. *Nature Reviews Neurology*, 11(8), 457–470.

Tcw, J., & Goate, A. M. (2017). Genetics of β -Amyloid Precursor Protein in Alzheimer's Disease. *Cold Spring Harbor Perspectives in Medicine*, 7(6), a024539.

Teich, A. F., Nicholls, R. E., Puzzo, D., Fiorito, J., Purgatorio, R., Fa', M., & Arancio, O. (2015). Synaptic therapy in Alzheimer's disease: a CREB-centric approach. *Neurotherapeutics: The Journal of the American Society for Experimental NeuroTherapeutics*, 12(1), 29–41.

Terry, A. V., & Buccafusco, J. J. (2003). The cholinergic hypothesis of age and Alzheimer's disease-related cognitive deficits: recent challenges and their implications for novel drug development. (Figura). *The Journal of Pharmacology and Experimental Therapeutics*, 306(3), 821–7.

Terry, R. D. and Davies, P. (1980) 'Dementia of the Alzheimer Type', *Annual Review of Neuroscience*, 3(1), pp. 77–95.

Thinakaran, G., & Koo, E. H. (2008). Amyloid precursor protein trafficking, processing, and function. *The Journal of Biological Chemistry*, 283(44), 29615–9.

- Tomlinson, D. R., & Gardiner, N. J. (2008). Glucose neurotoxicity. *Nature Reviews Neuroscience*, 9(1), 36–45.
- Tremblay, M. A., Acker, C. M., & Davies, P. (2010). Tau phosphorylated at tyrosine 394 is found in Alzheimer's disease tangles and can be a product of the Abl-related kinase, Arg. *Journal of Alzheimer's Disease : JAD*, 19(2), 721–33.
- Trinchese, F., Liu, S., Battaglia, F., Walter, S., Mathews, P. M., & Arancio, O. (2004). Progressive age-related development of Alzheimer-like pathology in APP/PS1 mice. *Annals of Neurology*, 55(6), 801–14.
- Trojanowski, J. Q., & Lee, V. M.-Y. (2005). Rous-Whipple Award Lecture. The Alzheimer's brain: finding out what's broken tells us how to fix it (Figura). *The American Journal of Pathology*, 167(5), 1183–1188.
- Troncone, L., Luciani, M., Coggins, M., Wilker, E. H., Ho, C.-Y., Codispoti, K. E., ... Del Monte, F. (2016). A β Amyloid Pathology Affects the Hearts of Patients With Alzheimer's Disease: Mind the Heart. *Journal of the American College of Cardiology*, 68(22), 2395–2407.
- Turner, A. J., Fisk, L., & Nalivaeva, N. N. (2004). Targeting amyloid-degrading enzymes as therapeutic strategies in neurodegeneration. *Annals of the New York Academy of Sciences*, 1035(1), 1–20.
- Turner, P. R., O'Connor, K., Tate, W. P., & Abraham, W. C. (2003). Roles of amyloid precursor protein and its fragments in regulating neural activity, plasticity and memory. *Progress in Neurobiology*, 70(1), 1–32.

U

Unzeta, M., Esteban, G., Bolea, I., Fogel, W. A., Ramsay, R. R., Youdim, M. B. H., ... Marco-Contelles, J. (2016). Multi-Target Directed Donepezil-Like Ligands for Alzheimer's Disease (Figura). *Frontiers in Neuroscience*, *10*, 205.

V

Valverde, A. M., Fabregat, I., Burks, D. J., White, M. F., & Benito, M. (2004). IRS-2 mediates the antiapoptotic effect of insulin in neonatal hepatocytes. *Hepatology (Baltimore, Md.)*, *40*(6), 1285–94.

Valverde, A. M., & González-Rodríguez, A. (2011). IRS2 and PTP1B: Two opposite modulators of hepatic insulin signalling. *Archives of Physiology and Biochemistry*, *117*(3), 105–15. <http://doi.org/10.3109/13813455.2011.557386>

Vandal, M., Alata, W., Tremblay, C., Rioux-Perreault, C., Salem, N., Calon, F., & Plourde, M. (2014a). Reduction in DHA transport to the brain of mice expressing human APOE4 compared to APOE2. *Journal of Neurochemistry*, *129*(3), 516–26.

Vandal, M., Bourassa, P., & Calon, F. (2015). Can insulin signaling pathways be targeted to transport A β out of the brain? *Frontiers in Aging Neuroscience*, *7*, 114.

Vandal, M., White, P. J., Tremblay, C., St-Amour, I., Chevrier, G., Emond, V., ... Calon, F. (2014b). Insulin reverses the high-fat diet-induced increase in brain A β and improves memory in an animal model of Alzheimer disease. *Diabetes*, *63*(12), 4291–301.

Van Dam, D., Coen, K., & De Deyn, P. (2010). Ibuprofen modifies cognitive disease progression in an Alzheimer's mouse model. *Journal of Psychopharmacology*, 24(3), 383–388.

Van der Flier, W. M., Pijnenburg, Y. AL, Fox, N. C., & Scheltens, P. (2011). Early-onset versus late-onset Alzheimer's disease: the case of the missing APOE ϵ 4 allele. *The Lancet Neurology*.

Van der Heide, L. P., Ramakers, G. M. J., & Smidt, M. P. (2006). Insulin signaling in the central nervous system: learning to survive. *Progress in Neurobiology*, 79(4), 205–21.

Van Marum, R. J. (2009). Update on the use of memantine in Alzheimer's disease. *Neuropsychiatric Disease and Treatment*, 5, 237–47.

W

Wang, J., Gu, B. J., Masters, C. L., & Wang, Y.-J. (2017). A systemic view of Alzheimer disease — insights from amyloid- β metabolism beyond the brain. *Nature Reviews Neurology*, 13(11), 703–703.

Wang, X., Zheng, W., Xie, J.-W., Wang, T., Wang, S.-L., Teng, W.-P., & Wang, Z.-Y. (2010). Insulin deficiency exacerbates cerebral amyloidosis and behavioral deficits in an Alzheimer transgenic mouse model. *Molecular*

Ward, A., Crean, S., Mercaldi, C. J., Collins, J. M., Boyd, D., Cook, M. N., & Arrighi, H. M. (2012). Prevalence of apolipoprotein E4 genotype and homozygotes (APOE ϵ 4/4) among patients diagnosed with Alzheimer's disease: a systematic review and meta-analysis. *Neuroepidemiology*, 38(1), 1–17.

Watson, G. S., & Craft, S. (2004). Modulation of memory by insulin and glucose: neuropsychological observations in Alzheimer's disease. *European Journal of Pharmacology*, 490(1–3), 97–113.

Wei, Y., Williams, J. M., Dipace, C., Sung, U., Javitch, J. A., Galli, A., & Saunders, C. (2007). Dopamine transporter activity mediates amphetamine-induced inhibition of Akt through a Ca²⁺/calmodulin-dependent kinase II-dependent mechanism. *Molecular Pharmacology*, 71(3), 835–42.

Weindruch, R., Walford, R. L., Fligiel, S., & Guthrie, D. (1986). The retardation of aging in mice by dietary restriction: longevity, cancer, immunity and lifetime energy intake. *The Journal of Nutrition*, 116(4), 641–54.

Weiner, M. W., Crane, P. K., Montine, T. J., Bennett, D. A., & Veitch, D. P. (2017). Traumatic brain injury may not increase the risk of Alzheimer disease. *Neurology*, 89(18), 1923–1925.

Weingarten, M. D., Lockwood, A. H., Hwo, S. Y., & Kirschner, M. W. (1975). A protein factor essential for microtubule assembly. *Proceedings of the National Academy of Sciences of the United States of America*, 72(5), 1858–62. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/1057175>

Welters, A., Lammert, E., Mayatepek, E., & Meissner, T. (2017). Need for Better Diabetes Treatment: The Therapeutic Potential of NMDA Receptor Antagonists. *Klinische Padiatrie*, 229(1), 14–20.

Weller, R. O., Subash, M., Preston, S. D., Mazanti, I., & Carare, R. O. (2008). Perivascular drainage of amyloid-beta peptides from the brain and its failure in cerebral amyloid angiopathy and Alzheimer's disease. *Brain Pathology (Zurich, Switzerland)*, 18(2), 253–66.

Wenk, G. L. (2006). Neuropathologic changes in Alzheimer's disease: potential targets for treatment. *The Journal of Clinical Psychiatry*, *67 Suppl 3*, 3–7; quiz 23.

Whitehouse, P. J. (1986). The concept of subcortical and cortical dementia: another look. *Annals of Neurology*, *19*(1), 1–6.

Whitehouse, P. J., Price, D. L., Struble, R. G., Clark, A. W., Coyle, J. T., & Delon, M. R. (1982). Alzheimer's disease and senile dementia: loss of neurons in the basal forebrain. *Science (New York, N.Y.)*, *215*(4537), 1237–9.

Wickelgren, I. (1998). Tracking insulin to the mind. *Science (New York, N.Y.)*, *280*(5363), 517–9.

Willette, A. A., Bendlin, B. B., Starks, E. J., Birdsill, A. C., Johnson, S. C., Christian, B. T., ... Asthana, S. (2015a). Association of Insulin Resistance With Cerebral Glucose Uptake in Late Middle-Aged Adults at Risk for Alzheimer Disease. *JAMA Neurology*, *72*(9), 1013–20.

Willette, A. A., Johnson, S. C., Birdsill, A. C., Sager, M. A., Christian, B., Baker, L. D., ... Bendlin, B. B. (2015b). Insulin resistance predicts brain amyloid deposition in late middle-aged adults. *Alzheimer's & Dementia : The Journal of the Alzheimer's Association*, *11*(5), 504–510.e1.

Winblad, B., Engedal, K., Soininen, H., Verhey, F., Waldemar, G., Wimo, A., ... Donepezil Nordic Study Group. (2001). A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. *Neurology*, *57*(3), 489–95.

Wisniewski, H. M., & Wegiel, J. (1991). Spatial relationships between astrocytes and classical plaque components. *Neurobiology of Aging*, *12*(5), 593–600.

Withers, D. J., Gutierrez, J. S., Towery, H., Burks, D. J., Ren, J. M., Previs, S., ... White, M. F. (1998). Disruption of IRS-2 causes type 2 diabetes in mice. *Nature*, *391*(6670), 900–4.

Witte, A. V., Fobker, M., Gellner, R., Knecht, S., & Floel, A. (2009). Caloric restriction improves memory in elderly humans. *Proceedings of the National Academy of Sciences*, *106*(4), 1255–1260.

Woods, S. C., & Porte, D. (1977). Relationship between plasma and cerebrospinal fluid insulin levels of dogs. *The American Journal of Physiology*, *233*(4), E331-4.

Woods, S. C., Seeley, R. J., Baskin, D. G., & Schwartz, M. W. (2003). Insulin and the blood-brain barrier. *Current Pharmaceutical Design*, *9*(10), 795–800.

X

Xiang, J. (2017). Carotid atherosclerosis promotes the progression of Alzheimer's disease: A three-year prospective study. *Experimental and Therapeutic Medicine*, *14*(2), 1321–1326.

Xiang, Y., Bu, X.-L., Liu, Y.-H., Zhu, C., Shen, L.-L., Jiao, S.-S., ... Wang, Y.-J. (2015). Physiological amyloid-beta clearance in the periphery and its therapeutic potential for Alzheimer's disease. *Acta Neuropathologica*, *130*(4), 487–99.

Xu, Q., Bernardo, A., Walker, D., Kanegawa, T., Mahley, R. W., & Huang, Y. (2006). Profile and regulation of apolipoprotein E (ApoE) expression in the CNS in mice with targeting of green fluorescent protein gene to the ApoE locus. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 26(19), 4985–94.

Y

Yankner, B. A., & Mesulam, M.-M. (1991). β -Amyloid and the Pathogenesis of Alzheimer's Disease. *New England Journal of Medicine*, 325(26), 1849–1857.

Z

Zempel, H., Thies, E., Mandelkow, E., & Mandelkow, E.-M. (2010). Abeta oligomers cause localized Ca(2+) elevation, missorting of endogenous Tau into dendrites, Tau phosphorylation, and destruction of microtubules and spines. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 30(36), 11938–50.

Zhang, B., Gaiteri, C., Bodea, L.-G., Wang, Z., McElwee, J., Podtelezhnikov, A. A., ... Emilsson, V. (2013). Integrated systems approach identifies genetic nodes and networks in late-onset Alzheimer's disease. *Cell*, 153(3), 707–20.

Zhang, F., & Jiang, L. (2015). Neuroinflammation in Alzheimer's disease. *Neuropsychiatric Disease and Treatment*, 11, 243–56.

Zhang, Y., Thompson, R., Zhang, H., & Xu, H. (2011). APP processing in Alzheimer's disease. *Molecular Brain*, 4(1), 3.

Zhang, Y., Zhou, B., Deng, B., Zhang, F., Wu, J., Wang, Y., ... Zhai, Q. (2013). Amyloid- β induces hepatic insulin resistance in vivo via JAK2. *Diabetes*, 62(4), 1159–66.

Zhao, J., O'Connor, T., & Vassar, R. (2011). The contribution of activated astrocytes to A β production: implications for Alzheimer's disease pathogenesis. *Journal of Neuroinflammation*, 8(1), 150.

Zhao, N., Liu, C.-C., Van Ingelgom, A. J., Martens, Y. A., Linares, C., Knight, J. A., ... Bu, G. (2017). Apolipoprotein E4 Impairs Neuronal Insulin Signaling by Trapping Insulin Receptor in the Endosomes. *Neuron*, 96(1), 115–129.e5.

Zhao, W., Chen, H., Xu, H., Moore, E., Meiri, N., Quon, M. J., & Alkon, D. L. (1999). Brain insulin receptors and spatial memory. Correlated changes in gene expression, tyrosine phosphorylation, and signaling molecules in the hippocampus of water maze trained rats. *The Journal of Biological Chemistry*, 274(49), 34893–902.

Zhao, Y., Wieman, H. L., Jacobs, S. R., & Rathmell, J. C. (2008). Chapter Twenty-Two Mechanisms and Methods in Glucose Metabolism and Cell Death. In *Methods in enzymology* (Vol. 442, pp. 439–457).

Zhao, Z., Xiang, Z., Haroutunian, V., Buxbaum, J. D., Stetka, B., & Pasinetti, G. M. (2007). Insulin degrading enzyme activity selectively decreases in the hippocampal formation of cases at high risk to develop Alzheimer's disease. *Neurobiology of Aging*, 28(6), 824–830.

