REVIEW

Potential preventive disease-modifying pharmacological strategies to delay late onset Alzheimer's disease

Miren Ettcheto[1, 2, 3, 4], **Oriol Busquets**[1, 2, 3, 4], **Antoni Camins**[1, 3, 4, *]

1 Departament de Farmacologia, Toxicologia i Química Terapèutica, Facultat de Farmàcia i Ciències de l'Alimentació, Universitat de Barcelona, Barcelona, Spain

2 Departament de Bioquímica i Biotecnologia, Facultat de Medicina i Ciències de la Salut, Universitat Rovira i Virgili, Reus, Spain

3 Institut de Neurociències, Universitat de Barcelona, Barcelona, Spain

4 Biomedical Research Networking Centre in Neurodegenerative Diseases (CIBERNED), Madrid, Spain

Funding: *The work was supported by the Spanish Ministry of Science and Innovation SAF2017-84283-R, PI2016/01, CB06/05/0024 (Biomedical Research Networking Centre in Neurodegenerative Diseases), and the European Regional Development Founds (all to AC).*

Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disease that was histopathologically characterized in the brain by the presence of extracellular senile plaques made of amyloid β peptides and intracellular neurofibrillary tangles composed of hyperphosphorylated Tau protein. Over the years, AD has been classified in two subgroups: early onset or familial AD and late onset or sporadic AD. On the one hand, familial AD has been described to be the result of genetic mutations that cause, in some cases, for the overproduction of amyloid β. On the other, the cause of late onset or sporadic AD is still unclear even though several hypotheses have been proposed to explain the process of severe and progressive memory and cognitive loss. In the present review, some of the current hypotheses that try to explain the origin of late onset or sporadic AD have been summarized. Also, their potential implication in the development of new drugs for the presymptomatic treatment of late onset or sporadic AD has been considered.

Key Words: *Alzheimer's disease; beta-secretase; neuroinflammation; Tau; amyloid; N-methyl-D-aspartate; glutamate*

***Correspondence to:**
Antoni Camins, PhD,
camins@ub.edu.

orcid:
0000-0002-1229-5956
(Antoni Camins)

doi: *10.4103/1673-5374.257513*

Received: *January 15, 2019*
Accepted: *March 27, 2019*

Introduction

After more than 100 years since Alzheimer's disease (AD) was first described, the scientific community has not been able to discover an effective molecule to modify or stop its progression (Hardy et al., 2014). Thus, the development of compounds to improve or alleviate neurodegeneration has become one of the major challenges for the future in the field of biomedicine (Cao et al., 2018).

In a recent review, all the drugs that are currently postulated as potentially effective to modify the evolution of AD have been summarized. From those, 26 are already on Phase III trials (Cummings et al., 2018) and, at least 50% of the total number of molecules that are currently under research are directly involved in the modulation of the amyloidogenic pathway. In **Figure 1**, some of the mechanisms in which amyloid beta (Aβ) is involved are depicted. It has been described that the oligomers promote microglial activation and promote neuroinflammation. Also, they can affect many other different intracellular organelles and pathways (mitochondria, endoplasmic reticulum, cell cycle, *etc*) that eventually lead to neuronal death and cognitive loss (Cline et al., 2018). The objective of Aβ-related treatments is the reduction of the levels of soluble oligomers by decreasing their production through the inhibition of beta-secretase (BACE-1) or gamma secretase or, by increasing the degradation and clearance of the oligomers. However, clinical trials with compounds like solanezumab, a humanized monoclonal antibody that recognizes soluble Aβ and increases its clearance from the brain, has failed to slow the clinical progression of mild-to-moderate AD patients (Honig et al., 2018). This data suggests that Aβ is not the only element involved in AD and it may actually be a cofactor that behaves as an aggravator while other alterations are the actual cause (Tse and Herrup 2017). Consequently, the fact that half of the research efforts are single-mindedly focused on the study of the amyloidogenic hypothesis does not favour the discovery of new beneficial therapies and strategies to treat and understand the disease. It is important to emphasise that 95% of AD cases are classified as sporadic or late-onset (LOAD) and, therefore, the previously mentioned drugs would only be potentially effective for the subtype labelled as genetic AD which accounts for the remaining 5%.

New research studies suggest that LOAD should be considered a disease with a multifactorial origin (Wijesekara et al., 2018). It is well known that aging is the main risk factor in its development, however, other mechanisms are involved in this process such as the production of reactive oxygen species in the mitochondria, the activation of the unfolded protein response in the endoplasmic reticulum and the upregulation of proinflammatory responses (Cummings et al., 2018; Swerdlow 2018). These alterations would

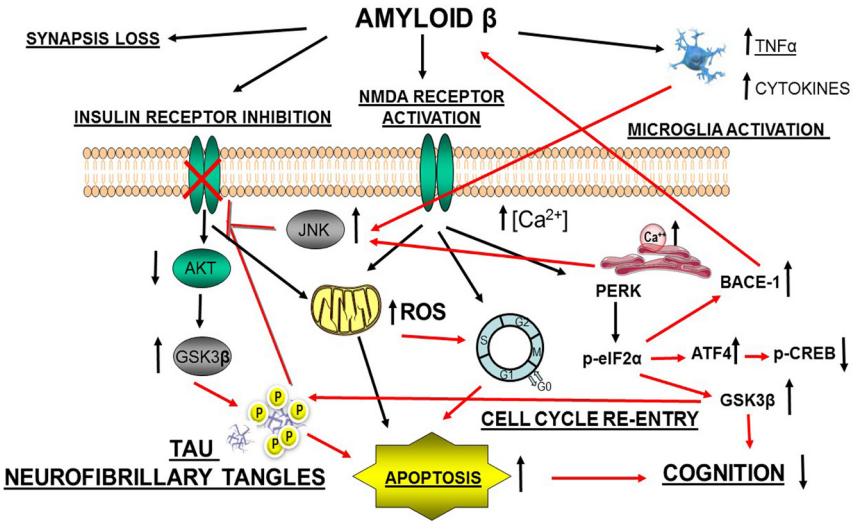

Figure 1 Schematic representation of potential molecular pathways involved in Aβ-induced brain neuronal apoptosis, microglial activation and cognitive affectation.
Aβ induces glial reactivity coupled with increased cytokine levels. TNFα activates JNK favoring IRS1 serine-inhibitory phosphorylation and posterior impaired insulin signaling. Alterations on normal activity of this axis also affects other downstream effectors like PI3K, PDK and AKT which are closely involved with synaptic function. Inhibition of AKT allows for activation of GSK3β, increasing abnormal Tau phosphorylation and posterior neuronal apoptosis. In addition, tyrosine residue phosphorylation by Aβ promotes insulin receptor internalization; exacerbating insulin signaling defects and promoting AD-related cognitive decline. Furthermore, Aβ induces prolonged endoplasmic reticulum stress and activation of the unfolded protein response (PERK/eIF2α/ATF4/CREB), which is also involved in cognitive loss phenomena. Finally, Aβ also promotes NMDA receptor activation, increase in cytosolic calcium levels and mitochondria and ER stress. In the end, all these alterations favor neuronal re-entry into the cell cycle and apoptosis. The relationship between the previously described mechanisms has been indicated in the figure by complete black and red arrows. Aβ: Amyloid beta; TNFα: tumor necrosis factor α; JNK: c-Jun N-terminal kinases; IRS-1: insulin receptor substrate; PI3K: phosphoinositide 3-kinase; PDK: phosphoinositide-dependent protein kinase; AKT: protein kinase B; GSK3β: glycogen synthase kinase 3β; PERK: protein kinase R-like endoplasmic reticulum kinase; eIF2α: eukaryotic initiation factor 2α; ATF4: activating transcription factor 4; CREB: cyclic adenosine monophosphate response element-binding protein; NMDA: N-methyl-D-aspartic acid.

favour cell cycle re-entry and the inhibition of autophagy, which would increase the accumulation of Aβ and the hyperphosphorylation of Tau. Thus, the key to treating LOAD will possibly be the result of the combination of multiple drugs that will modulate more than one molecular pathway at the same time (McDade and Bateman, 2017; Wenzel and Klegeris, 2018).

In the present review, we summarized available literature reviews found on the PubMed database. The search was not limited by any time period and was conducted between November 2018 and February 2019, with the objective to identify published peer-reviewed articles related to the topic in question in English. The collocated database search keywords were as follows: Alzheimer's disease AND type 2 diabetes, Neuroinflammation AND Alzheimer's disease, insulin AND cognitive decline, Alzheimer's disease treatments AND cognitive decline, Tau AND cognitive impairment, Tau AND Alzheimer's disease. The terms were searched using AND to combine the keywords listed and using OR to remove search duplication where possible.

The inclusion criteria were as follows: i) The period of the publishing of the article was limited by February, 2019. ii) Studies were only included from scientific journals in English. iii) The primary interest was focused on information about the delay of cognitive decline and Alzheimer's disease.

Alzheimer's Disease Treatments

Currently, acetylcholinesterase inhibitors and memantine are the only US Food and Drug Administration-approved drugs for the treatment of AD (Hampel et al., 2018). Acetylcholinesterase inhibitors increase acetylcholine levels by inhibiting the enzyme responsible of its degradation. This mechanism is expected to improve cognitive symptoms of AD by favouring the activation of cholinergic transmission even though, in advanced stages of the disease, accumulation of Aβ oligomers and glutamate cause overstimulation of glutamatergic receptors causing a massive entry of calcium into the cells and, as a result, excitotoxicity (Kodis et al., 2018). Recent studies have linked this pathological overstimulation with neuronal re-entry into the cell cycle by the activation of cyclins and cyclin-dependent kinases and posterior induction of apoptosis through the E2F-1 transcription factor. Memantine acts on the ionotropic receptors of glutamate, specifically the N-methyl-D-aspartic acid receptors, eliciting neuroprotective effects through its low-affinity antagonism. Nonetheless, neither of these drugs are effective on stopping the progression of the disease and only show temporary symptomatic improvements (Cao et al., 2018; Cummings et al., 2018). One of the hypothesis to explain the failure of the treatments until now is that their administration begins when the pathology

has already developed and, consequently, it is too late for it to have significant effects. Therefore, it is possible that a pre-emptive administration would have the desired effects that have been described in pre-clinical trials (McDade and Bateman, 2017).

Metabolic Hypothesis of Alzheimer's Disease

Other research groups have focused on the study of other hypotheses to understand the genesis of sporadic AD. For example, it has been described how resistance to insulin in the hippocampus favours cognitive loss (Ferreira et al., 2018). Thus, some research studies have postulated that LOAD should be considered a metabolic disease (Cardoso et al., 2017; Kang et al., 2017; Ferreira et al., 2018).

The first indications of this relationship were observed in the Rotterdam study where it was determined that type 2 diabetes mellitus patients showed a higher risk to suffer dementia than non-diabetic patients (Ott et al., 1996, 1999; Schrijvers et al., 2010). Also, research by Hoyer and colleagues had already described that the desensitization of the insulin receptor (IR) might be the reason for the onset of LOAD (Hoyer, 2002). This hypothesis states that the development of the pathology is due to the appearance of peripheral and central insulin resistance and it may be related to phenomena like obesity, which has been clearly associated with the appearance of cognitive decline. Likewise, it was reported that insulin resistance is associated with a decrease in brain glucose utilization in a late middle-age and can be used as a predictor for the eventual presence of Aβ deposition in multiple brain regions in middle-aged AD patients (Willette et al., 2015; McLimans et al., 2017). Other authors have described that Aβ can bind directly to hippocampal IR localized in postsynaptic terminals. These effects would further reinforce the idea that Aβ oligomers behave as pathology aggravators by inhibiting the activation of the IR or favoring its internalization (Bomfim et al., 2012; De Felice, 2013).

Thus, the amelioration of resistance in the IR would improve the cognitive process and synaptic function through the activation of protein kinase B (AKT), the inhibition of apoptosis and the modulation of mechanisms like the production of Aβ and neuroinflammation. Interestingly, several research studies have described beneficial effects on cognitive function after the use of antidiabetic drugs (De Felice et al., 2014; Ferreira et al., 2018).

For example, some studies administered intranasal insulin in AD patients. The aim was to improve cognition and brain glucose metabolism in people suffering from mild cognitive impairment or AD. However, results from that research study were not successful because continuous activation of the receptor by the hormone caused for its insensitization (De Felice et al., 2014, Clarke et al., 2015; Cardoso et al., 2017). Hence, several research groups concluded that the key is not in stimulating further the receptor but actually to modulate its activation through its regulatory mechanisms. The glucagon-like peptide-1 (GLP-1) receptor agonists such as exendin-4, liraglutide and lixisenatide, could be potential drugs able to improve the cognitive process in AD (Cardoso et al., 2017). The efficacy of liraglutide treatments have been evaluated in clinical trials and hopeful results in cognition activity have been reported. Glucose-dependent insulinotropic polypeptide (GIP) analogues such as D-Ala2-GIP are also under investigation and recently, it has been published that the development of dual peptide agonists GLP-1/glucagon and GLP-1/GIP and triagonists GLP-1/GCG/GIP is underway (Batista et al., 2019). Moreover, the anti-diabetic drug metformin has been described to be another suitable strategy to improve the cognitive process in LOAD (Markowicz-Piasecka et al., 2017). Several clinical trials are currently evaluating the potential efficacy of this drug in patients with mild cognitive impairment and AD (Cummings et al., 2018). It seems that metformin could improve slightly the cognitive process by favouring hepatic activity and improving insulin activity. Finally, thioazolidinediones are agonists of the peroxisome-proliferator activated receptors. Rosiglitazone and pioglitazone are examples of this group of drugs, which are also under investigation for the treatment of this disease (Cummings et al., 2018). Although preclinical studies suggest promising results, clinical studies with peroxisome-proliferator activated receptor γ agonists are required to confirm the potential efficacy of these molecules in improving brain insulin and insulin growth factor 1 resistance, as well as cognition in LOAD patients (Ferreira et al., 2018).

Neuroinflammatory Hypothesis of Alzheimer's Disease

Over the years, chronic neuroinflammation has been involved in synaptic dysfunctions. In preclinical models, it has been demonstrated that an obesogenic diet leads to loss of hippocampal synaptic plasticity, dendritic spine density and spatial memory through the phagocytosis of synaptic contacts due to increased microglia activity (De Felice et al., 2014; Hao et al., 2016; Rajendran and Paolicelli 2018). Furthermore, the release of cytokines such as tumor necrosis factor α favours cognitive loss through the activation of stress kinases such as the c-Jun N-terminal kinases (Vieira et al., 2018). These enzymes also favour the inactivation of the IR through the phosphorylation of the IR substrate at serine residues, blocking downstream insulin signalling.

Consequently, non-steroidal anti-inflammatory drugs should be considered as a potential strategy to treat neurodegenerative pathologies due to their relevant effect on systemic inflammatory processes (McGeer et al., 2018). These molecules are able to reduce microglial activation *via* canonical antiinflammatory pathways within the brain, decreasing cytokine levels and preventing synaptic loss by phagocytosis. Furthermore, non-steroidal anti-inflam-

matory drugs can modulate Aβ peptide formation in the brain through peroxisome-proliferator activated receptor γ activation and BACE-1 inhibition, as well as reduce Tau hyperphosphorylation (Ettcheto et al., 2017). Among the most studied non-steroidal anti-inflammatory drugs for the treatment of LOAD, ibuprofen, flurbiprofen and dexibuprofen should be considered while taking into account that neuroprotective effects through microglial inactivation only appear when drugs are administered before the appearance of clinical symptoms (in t' Veld et al., 2001).

Currently, a phase III clinical study on the combination of Cromolyn-Ibuprofen by AZ Therapies (Boston, MA, USA) is underway. The drug, namely ALZT-OP1, has a safe and tolerable profile and is aimed at treating patients with an early cognitive impairment (Cummings et al., 2018).

Tau Hypothesis of Alzheimer's Disease

Targeting Tau phosphorylation is another viable strategy for AD treatment. Preclinical studies suggest that cognitive loss is well related with an abnormal increase in Tau phosphorylation which, has been reported to have negative effects on metabolism (Marciniak et al., 2017). These results would further reinforce the hypotheses that define LOAD as a metabolic disease. Also, it supports other hypotheses that believe that these mechanisms work on systems based on positive feed-back cycles which would worsen progressively over time.

In a recent study, Preische and co-workers reported that the neurofilament light chain, a component of the axonal cytoskeleton expressed in myelinated axons, could be a suitable marker of brain damage and atrophy in preclinical models and neurodegenerative diseases (Preische et al., 2019). They suggest that neurofilament light chain levels could be mainly a fluid serum biomarker of disease progression and brain neurodegeneration at the early presymptomatic stages of familial AD. However, its clinically potential utility as biomarker in LOAD is unclear and may lead to confusion since it can also be altered by other pathologies.

TRx0237 is a Tau-related disease modifying drug in phase III clinical trials that is supposed to decrease neuronal damage mediated by Tau through the inhibition of its aggregation (Cummings et al., 2018).

Discussion

After taking into account some of this information, when considering the paradigm to understand LOAD, it is easy to picture that since the pathology has a multifactorial origin, it will require of more than one drug to treat it. Some researchers believe that the key will be found on the use of cocktails of different drugs, thus allowing for the modulation of different molecular mechanisms. Recent reports have also suggested that the administration of new hybrid compounds called multi-target-directed ligands might be an interesting approach (Wenzel and Klegeris 2018). New drug formulations may include N-methyl-D-aspartic acid antagonists, BACE-1 and acetylcholinesterase inhibitors and other modulators of the IR signalling pathway, neuroinflammatory responses and Tau aggregation (de la Monte et al., 2017; Cummings et al., 2018).

In addition, it is important to insist that current drugs show no significant therapeutic effects because they may be administered too late in the development of the pathology. So, it would be of high interest to determine early stage markers and indicators of the development of the pathology. As an example, recent studies have indicated that an increase of Aβ levels in saliva in LOAD patients can be detected (Lee et al., 2017). Some researchers have reported that treatments may need to be started pre-emptively 15 to 20 years before the actual appearance of clinical symptoms. Midlife may be a critical period for initiating treatments to improve peripheral IR signalling in order to maintain neural metabolism and cognitive function (Willette et al., 2015; Singh-Manoux et al., 2018).

To conclude, it is our belief that an effective AD preventive treatment shall include at least four drugs in a similar strategy to heart attack prevention.

Author contributions: *All the authors have participated in the drafting of the manuscript and have reviewed it.*
Conflicts of interest: *None of the authors has a conflict of interest.*
Financial support: *The work was supported by the Spanish Ministry of Science and Innovation SAF2017-84283-R, PI2016/01, CB06/05/0024 (Biomedical Research Networking Centre in Neurodegenerative Diseases), and the European Regional Development Founds (all to AC).*
Copyright license agreement: *The Copyright License Agreement has been signed by all authors before publication.*
Plagiarism check: *Checked twice by iThenticate.*
Peer review: *Externally peer reviewed.*

Open peer reviewers: *Beatrice Macchi, Universita degli Studi di Roma Tor Vergata, Italy; Ian Macreadie, RMIT University, Australia.*
Additional file: *Open peer review reports 1 and 2.*

References

Batista AF, Bodart-Santos V, De Felice FG, Ferreira ST (2019) Neuroprotective actions of glucagon-like peptide-1 (GLP-1) analogues in Alzheimer's and Parkinson's diseases. CNS Drugs 33:209-223.

Bomfim TR, Forny-Germano L, Sathler LB, Brito-Moreira J, Houzel JC, Decker H, Silverman MA, Kazi H, Melo HM, McClean PL, Holscher C, Arnold SE, Talbot K, Klein WL, Munoz DP, Ferreira ST, De Felice FG (2012) An anti-diabetes agent protects the mouse brain from defective insulin signaling caused by Alzheimer's disease- associated Aβ oligomers. J Clin Invest 122:1339-1353.

Cao J, Hou J, Ping J, Cai D (2018) Advances in developing novel therapeutic strategies for Alzheimer's disease. Mol Neurodegener 13:64.

Cardoso S, Seiça R, Moreira PI (2017) Diabesity and brain energy metabolism: the case of Alzheimer's disease. Adv Neurobiol 19:117-150.

Clarke JR, Lyra E Silva NM, Figueiredo CP, Frozza RL, Ledo JH, Beckman D, Katashima CK, Razolli D, Carvalho BM, Frazão R, Silveira MA, Ribeiro FC, Bomfim TR, Neves FS, Klein WL, Medeiros R, LaFerla FM, Carvalheira JB, Saad MJ, Munoz DP, et al. (2015) Alzheimer-associated Aβ oligomers impact the central nervous system to induce peripheral metabolic deregulation. EMBO Mol Med 7:190-210.

Cline EN, Bicca MA, Viola KL, Klein WL (2018) The amyloid-β oligomer hypothesis: beginning of the third decade. J Alzheimers Dis 64:S567-610.

Cummings J, Lee G, Ritter A, Zhong K (2018) Alzheimer's disease drug development pipeline: 2018. Alzheimers Dement (N Y) 4:195-214.

De Felice FG, Lourenco MV, Ferreira ST (2014) How does brain insulin resistance develop in Alzheimer's disease? Alzheimers Dement 10:S26-32.

De Felice FG (2013) Alzheimer's disease and insulin resistance: translating basic science into clinical applications. J Clin Invest 123:531-539.

de la Monte SM (2017). Insulin resistance and neurodegeneration: progress towards the development of new therapeutics for Alzheimer's disease. Drugs 77:47-65.

Ettcheto M, Sánchez-López E, Pons L, Busquets O, Olloquequi J, Beas-Zarate C, Pallas M, García ML, Auladell C, Folch J, Camins A (2017) Dexibuprofen prevents neurodegeneration and cognitive decline in APPswe/PS1dE9 through multiple signalling pathways. Redox Biol 13:345-352.

Ferreira LSS, Fernandes CS, Vieira MNN, De Felice FG (2018) Insulin resistance in Alzheimer's disease. Front Neurosci 12:830.

Hardy J, Bogdanovic N, Winblad B, Portelius E, Andreasen N, Cedazo-Minguez A, Zetterberg H (2014) Pathways to Alzheimer's disease. J Intern Med 275:296-303.

Hampel H, Vergallo A, Aguilar LF, Benda N, Broich K, Cuello AC, Cummings J, Dubois B, Federoff HJ, Fiandaca M, Genthon R, Haberkamp M, Karran E, Mapstone M, Perry G, Schneider LS, Welikovitch LA, Woodcock J, Baldacci F, Lista S, et al. (2018) Precision pharmacology for Alzheimer's disease. Pharmacol Res 130:331-365.

Hao S, Dey A, Yu X, Stranahan AM (2016) Dietary obesity reversibly induces synaptic stripping by microglia and impairs hippocampal plasticity. Brain Behav Immun 51:230-239.

Hoyer S (2002) The brain insulin signal transduction system and sporadic (type II) Alzheimer disease: an update. J Neural Transm 109:341-360.

Honig LS, Vellas B, Woodward M, Boada M, Bullock R, Borrie M, Hager K, Andreasen N, Scarpini E, Liu-Seifert H, Case M, Dean RA, Hake A, Sundell K, Poole Hoffmann V, Carlson C, Khanna R, Mintun M, DeMattos R, Selzler KJ, et al. (2018) Trial of Solanezumab for mild dementia due to Alzheimer's disease. N Engl J Med 378:321-330.

in t' Veld BA, Ruitenberg A, Hofman A, Launer LJ, van Duijn CM, Stijnen T, Breteler MM, Stricker BH (2001) Nonsteroidal antiinflammatory drugs and the risk of Alzheimer's disease. N Engl J Med 345:1515-1521.

Kang S, Lee YH, Lee JE (2017) Metabolism-centric overview of the pathogenesis of Alzheimer's disease. Yonsei Med J 58:479-488.

Kodis EJ, Choi S, Swanson E, Ferreira G, Bloom GS (2018) N-Methyl-D-aspartate receptor-mediated calcium influx connects amyloid-β oligomers to ectopic neuronal cell cycle reentry in Alzheimer's disease. Alzheimers Dement 14:1302-1312.

Lee M, Guo JP, Kennedy K, McGeer EG, McGeer PL (2017) A method for diagnosing Alzheimer's disease based on salivary amyloid-β protein 42 levels. J Alzheimers Dis 55:1175-1182.

Marciniak E, Leboucher A, Caron E, Ahmed T, Tailleux A, Dumont J, Issad T, Gerhardt E, Pagesy P, Vileno M, Bournonville C, Hamdane M, Bantubungi K, Lancel S, Demeyer D, Eddarkaoui S, Vallez E, Vieau D, Humez S, Faivre E, et al. (2017) Tau deletion promotes brain insulin resistance. J Exp Med 214:2257-2269.

Markowicz-Piasecka M, Sikora J, Szydłowska A, Skupień A, Mikiciuk-Olasik E, Huttunen KM (2017) Metformin - a future therapy for neurodegenerative diseases. Pharm Res 34:614-2627.

McDade E, Bateman RJ (2017) Stop Alzheimer's before it starts. Nature 547:153-155.

McGeer PL, Guo JP, Lee M, Kennedy K, McGeer EG (2018) Alzheimer's disease can be spared by nonsteroidal anti-inflammatory drugs. J Alzheimers Dis 62:1219-1222.

McLimans KE, Webb JL, Anantharam V, Kanthasamy A, Willette AA (2017) Alzheimer's disease neuroimaging initiative. Peripheral versus central index of metabolic dysfunction and associations with clinical and pathological outcomes in Alzheimer's disease. J Alzheimers Dis 60:1313-1324

Ott A, Stolk RP, Hofman A, van Harskamp F, Grobbee DE, Breteler MM (1996) Association of diabetes mellitus and dementia: The Rotterdam Study. Diabetologia 39:1392-1397.

Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM (1999) Diabetes mellitus and the risk of dementia: The Rotterdam Study. Neurology 53:1937-1942.

Preische O, Schultz SA, Apel A, Kuhle J, Kaeser SA, Barro C, Gräber S, Kuder-Buletta E, LaFougere C, Laske C, Vöglein J, Levin J, Masters CL, Martins R, Schofield PR, Rossor MN, Graff-Radford NR, Salloway S, Ghetti B, Ringman JM, et al. (2019) Dominantly Inherited Alzheimer Network. Serum neurofilament dynamics predicts neurodegeneration and clinical progression in presymptomatic Alzheimer's disease. Nat Med 25:277-283.

Rajendran L, Paolicelli RC (2018) Microglia-mediated synapse loss in Alzheimer's disease. J Neurosci 38:2911-2919.

Schrijvers EM, Witteman JC, Sijbrands EJ, Hofman A, Koudstaal PJ, Breteler MM (2010) Insulin metabolism and the risk of Alzheimer disease: The Rotterdam Study. Neurology 75:1982-1987.

Singh-Manoux A, Dugravot A, Shipley M, Brunner EJ, Elbaz A, Sabia S, Kivimaki M (2018) Obesity trajectories and risk of dementia: 28 years of follow-up in the Whitehall II Study. Alzheimers Dement 14:178-186.

Swerdlow RH (2018) Mitochondria and mitochondrial cascades in Alzheimer's disease. J Alzheimers Dis 62:1403-1416.

Tse KH, Herrup K (2017) Re-imagining Alzheimer's disease - the diminishing importance of amyloid and a glimpse of what lies ahead. J Neurochem 143:432-444.

Vieira MNN, Lima-Filho RAS, De Felice FG (2018) Connecting Alzheimer's disease to diabetes: Underlying mechanisms and potential therapeutic targets. Neuropharmacology 136:160-171.

Wenzel TJ, Klegeris A (2018) Novel multi-target directed ligand-based strategies for reducing neuroinflammation in Alzheimer's disease. Life Sci 207:314-322.

Wijesekara N, Gonçalves RA, De Felice FG, Fraser PE (2018) Impaired peripheral glucose homeostasis and Alzheimer's disease. Neuropharmacology 136:172-181.

Willette AA, Johnson SC, Birdsill AC, Sager MA, Christian B, Baker LD, Craft S, Oh J, Statz E, Hermann BP, Jonaitis EM, Koscik RL, La Rue A, Asthana S, Bendlin BB (2015) Insulin resistance predicts brain amyloid deposition in late middle-aged adults. Alzheimers Dement 11:504-510.

P-Reviewer: Francisco-Morcillo J; C-Editors: Zhao M, Yu J; T-Editor: Jia Y