Frontiers in Neuroendocrinology 52 (2019) 1–11

Contents lists available at ScienceDirect

Frontiers in Neuroendocrinology

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

Review article

Adiponectin and sporadic Alzheimer's disease: Clinical and molecular links

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ARTICLE INFO

Keywords:
Obesity
BMI
Adipokine
Adiponectin
Memory
Cognition
Dementia
Alzheimer's disease

ABSTRACT

Obesity has been consistently associated with Alzheimer's disease (AD) though the exact mechanisms by which it influences cognition are still elusive and subject of current research. Adiponectin, the most abundant adipokine in circulation, is inversely correlated with adipose tissue dysfunction and seems to be a central player in this association. In fact, different signalling pathways are shared by adiponectin and proteins involved in AD pathophysiology and considerable amount of evidence supports its direct and indirect influence on β-amyloid and tau aggregates formation. In this paper we present a critical review of cellular, animal and clinical studies which have contributed to a more thorough understanding of the extent to which adiponectin influences the risk of developing AD as well as its progression. Finally, the effect of acetylcholinesterase inhibitors on circulating adiponectin levels, possible therapeutic applications and future research strategies are also discussed.

1. Introduction

Alzheimer's disease (AD) is currently the sixth-leading cause of death in the United States as well as a major cause of morbidity and economical burden worldwide. AD is a slowly progressive central nervous system (CNS) disease, characterized pathologically by a dysfunction of amyloid precursor protein (APP) processing leading to deposition of β-amyloid and tau hyperphosphorylation that culminates in neuronal death (Alzheimer's Association, 2016). Even though these pathological events are confined to the brain, growing evidence supports the vulnerability of the hippocampus and other structures involved in cognition to systemic metabolic abnormalities (Chakrabarti et al., 2015). Several clinical and experimental studies have supported the hypothesis that neurodegenerative disorders often coexist with metabolic dysfunction, which can exacerbate or even trigger central harmful signalling pathways (Cai et al., 2012). The interface between obesity and AD is a good example of this complex crosstalk between central and systemic compartments.

2. Search strategy and selection criteria

For this review we searched PubMed database for the terms "adiponectin", "adipokine" or "obesity" AND "dementia", "Alzheimer", "mild cognitive impairment", "memory", "cognition" or "hippocampus" within the article title or abstract, irrespective of the year of publication. We also searched for studies reporting an "association between adiponectin and Alzheimer's disease or cognitive impairment". Only articles published in English were considered. Selection was based on the quality and relevance of the papers to our main objective - to provide a critical review of the most relevant research on the association between adiponectin and AD, exploring potential mechanisms that bridge peripheral and central pathophysiological signalling pathways and possible therapeutic implications.

3. Adiponectin

Obesity prevalence has been globally increasing at an alarming rate and is estimated that nearly 40% of adults worldwide are currently overweight (WHO, 2008). This epidemic has focus researchers' attention on the biology of dysfunctional adipose tissue (Fig. 1), especially visceral white adipose tissue (WAT), and its adipokine-mediated signalling pathways (Kiliaan et al., 2014). The term adipokine (*adipokinos*: adipose tissue-movement) includes dozens of cell-signalling polypeptides secreted by WAT such as cytokines, acute phase reactants,

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http://dx.doi.org/10.1016/j.yfrne.2017.10.002
Received 13 June 2017; Received in revised form 5 September 2017; Accepted 10 October 2017
Available online 13 October 2017
0091-3022/

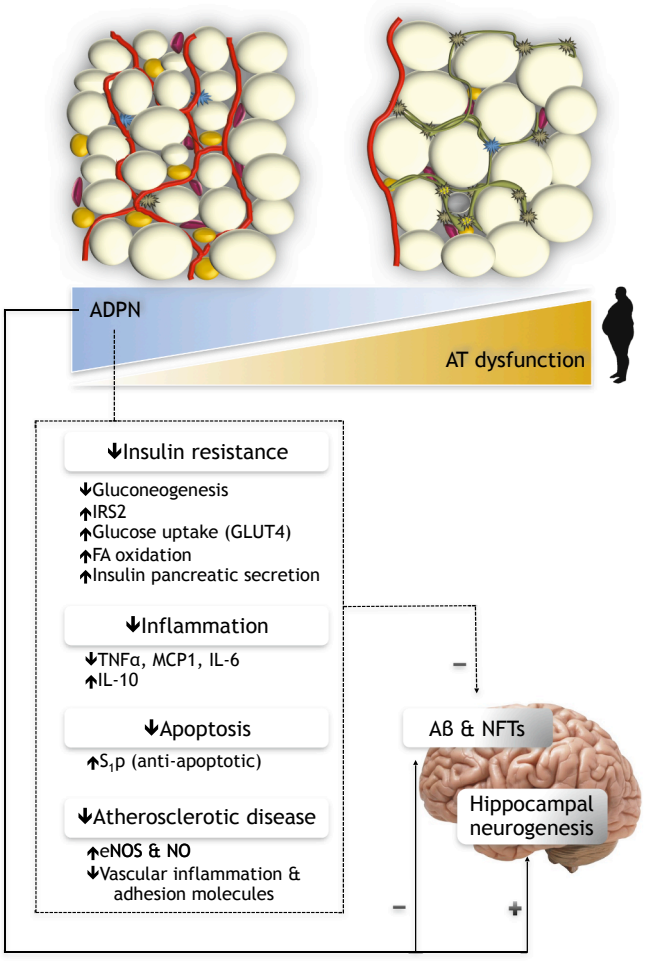

Fig. 1. Obesity-associated adipose tissue dysfunction influences Alzheimer's disease pathology through an altered adiponectin secretion. Obesity-associated adipose tissue (AT) dysfunction is characterized by an imbalance between energy intake and expenditure. Consequently, recruitment of M1 macrophages, with elevated M1 (in green)/M2 (in blue) ratio, impaired adipogenesis (yellow and small adipocytes), enhanced adipocyte hypertrophy and apoptosis (black and small adypocyte), impaired vascularization with consequent hypoxia, and excess deposition of extracellular matrix proteins (in green) will progressively occur. These alterations in immune, vascular, and structural AT composition will, in turn, result in an altered secretoma, including decreased production of adiponectin (ADPN). Therefore, peripheral and central beneficial effects of this adipokine become compromised. Its insulin-sensitizing, anti-inflammatory, anti-apoptotic and anti-atherosclerotic properties can indirecly (dashed line) counterbalance Alzheimer's Disease pathology, altough direct effects (solid line) on hippocampal neurogenesis and on Aβ (amyloid β) and tau (NFT, neurofibrillary tangles) metabolism have also been described.

inflammatory mediators, hormones and other chemical messengers (Pardo et al., 2012). Adiponectin (ADPN), a collagen-like 30 kDa protein, is the most abundant adipokine in circulation, representing 0.01% of total serum proteins in humans and up to 0.05% in rodents (85% of homology exists between human and murine ADPN isoforms) (Turer and Scherer, 2012). It is considered an adipose tissue-specific protein, though very small amounts can be synthetized by other cell types, and its circulating levels are paradoxically decreased with increasing central adiposity (Scherer et al., 1995; Turer and Scherer, 2012). ADPN circulates in its full-lenght form (fAd) or as a proteolytic fragment that corresponds to a globular domain (gAd), but also as trimers, hexamers or as high molecular weight (HMW) forms, and, according to current knowledge, exerts its effects by binding to specific receptors. To date, three ADPN receptors have been identified: AdipoR1, AdipoR2 and T-cadherin (T-cad). The first two, which homology between human and mice is superior to 95% (Yamauchi et al., 2014), are highly structurally related and ubiquitously expressed, though with variable affinity to different isoforms and variable predominance in some tissues. The activation of signalling cascades seems also dependent on the specific localization of these receptors. In the brain, AdipoRs are widely expressed, with AdipoR1 expression being more pronounced. In humans, they have been localized in the hypothalamus, pituitary gland and also in the nucleus basalis of Meynert and in the hippocampus (Thundyil et al., 2012), two of the main targeted structures in AD. T-cad, which lacks an intracellular domain, is also present in the hippocampus and studies with T-cad knockout mice show that it plays an important, but still elusive, role in cognitive circuits (Rivero et al., 2015). Despite its much lower cerebrospinal fluid (CSF) concentration (1000×), there is a good correlation between CSF and serum ADPN concentration, (Hietaharju et al., 2010; Kusminski et al., 2007; Une et al., 2011), which favors blood brain barrier (BBB) crossing as the major source of cerebral ADPN, although intrathecal synthesis of this adipokine has not been ruled out.

The list of beneficial metabolic effects of ADPN is extensive. It includes widely accepted systemic insulin-sensitizing and anti-atherosclerotic properties (Fig.1), although its anti-inflammatory role is questionable and may depend on the isoform, specific tissue it acts on and the presence or absence of disease (Thundyil et al., 2012). Additionally, anticancer and neuroprotective effects have been demonstrated, though much still remains to be elucidated in these areas (Brochu-Gaudreau et al., 2010; Turer and Scherer, 2012).

4. Adiponectin and Alzheimer's disease

While low circulating ADPN levels have been consistently associated with ischemic cerebrovascular disease, its role in neurodegenerative diseases is less well established (Ishii and Iadecola, 2016; Yang et al., 2015). Nevertheless, it is our conviction that AD is a brain metabolic disorder whose natural history may intrinsically be linked to adipose tissue physiology. The next sections will provide an extensive review of the existent literature regarding the role of ADPN in this specific disorder and possible therapeutic applications, hoping to encourage research in this field.

4.1. Current state of clinical research

Evidence from clinical studies aiming to assess the contribution of ADPN to the risk of developing AD or to its progression is listed in Table 1.

Overall, the involvement of ADPN in AD is poorly understood, with divergent results showing a decrease (Gorska-Ciebiada et al., 2016; Kamogawa et al., 2010; Teixeira et al., 2013), increase (Khemka et al., 2014; Une et al., 2011; van Himbergen et al., 2012; Waragai et al., 2016; Wennberg et al., 2016), or no significant changes (Bigalke et al., 2011; Diniz et al., 2012; Dukic et al., 2015; Gu et al., 2010; Kitagawa et al., 2015; Roberts et al., 2009; Warren et al., 2012) in the concentration of this adipokine in different stages of the disease (mild cognitive impairment - MCI vs AD) or when patients are compared to cognitively normal controls. At present, the only meta-analysis assessing the correlation between ADPN and AD, which includes 5 studies comprising a total of 727 subjects (254 AD and 473 controls), shows higher peripheral levels of ADPN in AD patients when compared to controls (Ma et al., 2016).

Detailed analysis of the observational studies presented unveils substantial caveats that contribute to the incongruences described above. One of the most important is patient selection, or more specifically, diagnostic accuracy. The inclusion of non-AD dementias and the etiological diversity of MCI groups definitely contribute to the heterogeneity of the cohorts. In fact, MCI is a clinical entity and not all cases translate a prodromal phase of AD. The incorporation of biomarker information in the diagnostic process is therefore essential to distinguish those related to AD from non-AD or nondegenerative cases, but surprisingly, few studies include them in the classification of patients.

Table 1
Population-based studies aiming to assess the association between adiponectin and Alzheimer's disease. Aβ: amyloid beta; AD: Alzheimer's Disease; ADPN: Adiponectin; aMCI: amnesic Mild Cognitive Impairment; AMNART: American National Adult Reading Test; ApoE: Apolipoprotein E; AVLT: Auditory Verbal Learning Test; BADL: Basic Activities Of Daily Living (Katz); BDAE: Boston Diagnostic Aphasia Evaluation; BMI: Body Mass Index; BNT: Boston Naming Test; BVRT: Benton Visual Retention Test; CAMCOG: Cambridge Cognitive Test; CDT: Clock Drawing Test; CI: Cognitive Imparment; CLEIA: chemiluminescence enzyme immunoassayCSF: Cerebrospinal Fluid; DHA: Docosahexaenoic Acid; DM: Diabetes Mellitus; DS: Digit Span; ELISA: Enzyme-Linked Immunosorbent Assay; FDG-PET: Fludeoxyglucose-Positron Emission Tomography; FOME: Fuld Object Memory Evaluation; HDSR: Hasegawa Dementia Scale Revised; HMW: high molecular weight; HT: hypertension; IADL: Instrumental Activities Of Daily Living (Lawton); IH: Immunohistochemistry; ITA: Immunoturbidimetric Assay; J-SHIPP: Japanese-Shimanami Health Promoting Program; LLD: Late-Life Depression; LMVR: Logical Memory And Visual Reproduction; MCI: Mild Cognitive Impairment; MCSA: Mayo Clinic Study Of Aging; MDRS: Mattis Dementia Rating Scale; MMSE: Mini-Mental State Examination; mo: months; MOANS: Mayo Older Americans Normative Studies; MoCA: Montreal Cognitive Assessment; naMCI: non amnesic-Mild Cognitive Impairment; NC: Normal Cognition/Control; NI: No Information; noCI: No Cognitive Impairment; OR: Odds Ratio; OSACA2: Osaka Follow-Up Study For Carotid Atherosclerosis, Part 2; RBMT: Rivermead Behavioral Memory Test; RDT: Rosen Drawing Test; RIA: Radioimmunoassay; SCT: Short Cognitive Test; SRT: Selective Reminding Test; TARCC: Texas Alzheimer's Disease Research And Care Consortium; TMT: Trail Making Test; VFT: Verbal Fluency Test; WAIS-R: Wechsler Adult Intelligence Scale-Revised; WHICAP: Washington Heights Inwood Columbia Aging Project; WHR: Waist-Hip Ratio; WMD: Weighted Mean Difference; WMS-R: Wechsler Memory Scale-Revised; y = years. ♂: male, ♀: female.

Study, country of origin	First author, year	n	Age	Sex	Follow-up	ApoE	Cognitive assessment	Sample (method)	Results
Rochester Epidemiology Project, USA	Roberts, 2009	747 NC	79.8 (75.0, 83.7)[a]	333 ♂/414 ♀	0	Yes	MOANS	Plasma (RIA)	Total ADPN is **similar** in MCI and NC [MCI = 14.4 (9.8, 19.6) vs NC = 14.5 (9.8, 19.6) mg/L; p = .97],[a] though OR of naMCI was 2.5 in the lowest compared to the highest quartile of ADPN (95%CI: 0.85–7.73)
		143 MCI	82.0 (78.2, 85.7)[a]	76 ♂/67 ♀					Adjustments: age, gender, education, ApoE, comorbidities
J-SHIPP Study, Japan	Kamogawa, 2010	397 NC	67 (62, 72)[a]	123 ♂/274♀	0	No	MCI Screen	Plasma (ELISA)	A 10 mg/l increase in total ADPN was associated with a 54% **reduction in OR** for MCI in men (OR: 0.46; 95%CI: 0.20–0.97; p = .041)
		120 MCI	72 (68, 77)[a]	56 ♂/64 ♀			HDSR		Adjustments: age, subcutaneous abdominal fat area
WHICAP II, USA	Gu, 2010	1219 NC	76.7 ± 6.4[b]	407 ♂/812 ♀	3.8 ± 1.3y	Yes	SRT, BNT, VFT, BVRT, RDT, Similarities test (WAIS-R), Identities & Oddities (MDRS), Repetition & Comprehension (BDAE)	Serum (RIA)	Total ADPN was **not associated** with baseline cognitive score nor associated with AD risk [incident AD (n = 118) = 10.2 (6.8–18.5)[a]; dementia-free (n = 1101) = 11.3 (7.0–18.0)[a] μg/ml, p = .75)] Adjustments: age, gender, race, education and cohort
Clinical series, Germany	Bigalke, 2011	37 NC	67.3 ± 10.2[b]	19 ♂/18 ♀	0	No	MMSE	Plasma (ELISA)	Total ADPN levels did not show **any significant difference** between groups (AD = 18.5 ± 18.1 vs. NC = 16.7 ± 8.9 μg/mL; p = .641)
		41 AD	74.3 ± 9.1[b]	19 ♂/22 ♀					
Clinical series, Japan	Une, 2011	28 NC	72.5 ± 2.82[b]	12 ♂/16 ♀	0	Yes	MMSE	Plasma + CSF (ELISA)	Total ADPN was significantly **higher** in MCI and AD compared to NC (p < .05); CSF ADPN was significantly **higher** in MCI compared to NC (p < .05); when ADPN levels were normalized to body weight only the difference between MCIvsNC and ADvsNC remained significant. Plasma and CSF ADPN levels showed a positive correlation (r = 0.406, p = .005)
		18 aMCI	74.2 ± 2.16[b]	9 ♂/9 ♀					Adjustments: age, gender
		27 AD	77.4 ± 0.95[b]	8 ♂/19 ♀					
TARCC, USA	Warren, 2012	197 NC	70 (38)[c]	61 ♂/136 ♀	0	Yes	MMSE, DS, TMT, BNT, LMVR VFT, CDT, AMNART	Serum (NI)	Total ADPN levels were **similar** between the two groups (NC = 5.1 ± 18 vs AD = 5.75 ± 32 μg/ml; p = .101)
		150 AD	79.5 (37)[c]	45 ♂/105 ♀					Adjustments: age, education
Clinical series, Brazil	Diniz, 2012	51 NC	68.7 ± 5.6[b]	11 ♂/40 ♀	0	No	MMSE CAMCOG	Serum (ELISA)	**No significant difference** was observed in ADPN levels between LLD subgroups (LLD-CI: 55005.26 ± 3616.78; LLD-noCI: 54422.06 ± 4469.64 pg/mL; p = .6) though reduced in LLD when compared with NC; ADPN levels were positively correlated with language (r = 0.44; p < .001) and calculation (r = 0.23, p = .02), as well as abstraction, attention and praxis, but not with memory or orientation
		47 LLD (32CI;15noCI)	70.2 ± 4.7[b]	10 ♂/37 ♀					
Framingham Heart Study, USA	van Himbergen, 2012	826 NC	72 ± 4[b] (♂)	299 ♂/541 ♀	13 y	Yes	MMSE	Plasma (ITA)	Total ADPN was associated with an **increased risk** of all-cause dementia (HR 1.29; 95%CI: 1.00–1.66; p = .054) and AD (HR = 1.33; 95%CI: 1.00–1.76; p = .050) only in women (by 1-SD increase in ADPN concentration)
			73 ± 4[b] (♀)						Adjustments: age, BMI, weight change, ApoE, education, plasma DHA

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Table 1 (*continued*)

Study, country of origin	First author, year	n	Age	Sex	Follow-up	ApoE	Cognitive assessment	Sample (method)	Results
Clinical series, Brazil	Teixeira, 2013	51 NC	68.7 ± 5.6[b]	10 ♂/41 ♀	34.6 ± 13.2 m	Yes	CAMCOG	Serum (ELISA)	Total ADPN levels were significantly **lower** in MCI and AD when compared to NC (MCI = 52898.69 ± 7651.59; AD = 52145.53 ± 7431.62; NC = 63337.38 ± 4233.84 pg/ml; $p < .001$) and **did not predict progression** from NC to MCI or from MCI to AD (F = 2.8; df = 1, $p = .1$). ADPN inversely correlated with TMT B (r = −0.325, $p = .002$); the correlation between CAMCOG, RBMT and FOME total scores showed a trend toward significance (r = 0.195, $p = .06$; r = 0.198, $p = .06$; r = 0.199, $p = .06$, respectively)
		65 aMCI 41 AD	71.1 ± 13.4[b] 75.4 ± 7.9[b]	17 ♂/48 ♀ 14 ♂/27 ♀	26.4 ± 17.4 m 0		MMSE, SCT, RBMT, FOME, TMT, CDT, VFT		Adjustments: age, education, ApoE, BMI, comorbidities
Clinical series, India	Khemka, 2014	60 NC 60 AD	64.75 ± 4.40[b] 66.97 ± 6.36[b]	34 ♂/26 ♀ 33 ♂/27 ♀	0	No	MMSE	Serum (ELISA)	Total ADPN levels were significantly **elevated** in AD compared to NC (33.33 ± 17.28 vs 8.27 ± 3.0 μg/ml; $p < .001$) and showed a negative correlation with MMSE score in AD subjects (r = −0.5236; $p < .0001$)
Clinical series, Croatia	Dukic, 2015	50 NC 48 MCI 70 AD	66 (63–73)[c] 72 (68–76)[c] 74 (69–79)[c]	20 ♂/30 ♀ 17 ♂/31 ♀ 20 ♂/30 ♀	0	No	MMSE MoCA	Serum (ITA)	Concentration of total ADPN **did not differ** between groups [AD: 10.6 (8.4–13.8); MCI: 10.4 (7.7–14.8); NC: 8.8 (5.8–13.3) μg/ml; $p = .268$]
OSACA2, Japan	Kitagawa, 2015	466 NC	67.8 ± 8.3[b]	275 ♂/191 ♀	6.9 y (NI)[b]	Yes	MMSE	Serum (CLEIA)	Risk of AD was **identical** in patients with high vs low HMW- ADPN levels ($p = .740$; cut-off: 3.47 μg/ml); no association with medial temporal lobe atrophy Adjustments: age, gender, education, ApoE, baseline MMSE, vascular risk factors and cerebrovascular events
Clinical Series, Poland	Gorska-Ciebiada, 2016	132 NC	72.5 ± 4.9[b]	82 ♂/50 ♀	0	No	MoCA	Serum (ELISA)	Concentration of total ADPN was **lower** in diabetic MCI vs diabetic controls (BMI 26–27.9: 9.37 ± 3.33 vs 11.76 ± 3.05, p = .009; BMI 28–29.9: 6.14 ± 2.85 vs10.38 ± 2.77, p < .001; BMI ≥ 30: 2.89 ± 1.59 vs 5.44 ± 3.78 μg/ml p < .001). ADPN negatively correlated with MoCA score (r = −0.3, $p = .016$)
		62 MCI (all DM2)	74.7 ± 3.9[b]	30 ♂/32 ♀			BADL IADL		Adjustments: BMI
Clinical series, China	Ma, 2016	91 NC	80.03 ± 8.32[b]	37 ♂/54 ♀	0	No	MMSE	Serum (ELISA)	**Higher level** of total ADPN were found in AD (NC: 8.21 ± 0.42 vs AD: 14.51 ± 1.00 μg/ml; $p < .0001$) ADPN levels showed significant inverse correlation with MMSE score in AD subjects (r = −0.518, $p < .01$) Adjustments: MMSE (cut-off 15), gender Meta-analysis result: pooled WMD of ADPN levels in AD vs NC = 9.42 μg/mL (95%CI: 4.21, 14.62)
		91 AD	82.96 ± 9.33[b]	36 ♂/55 ♀					
Clinical series, Japan	Waragai, 2016	62 NC	76.0 ± 7.9[b]	34 ♂/28 ♀	0	Yes	MMSE	Serum and CSF (ELISA)	Total serum ADPN was significantly **higher** in patients with MCI and AD compared to NC (MCI: $p < .05$, AD: $p < .001$), whereas CSF ADPN was significantly lower in patients with AD compared to those with MCI and NC ($p < .001$)
		64 MCI 63 AD	76.0 ± 6.5[b] 78.8 ± 6.1[b]	24 ♂/40 ♀ 21 ♂/42 ♀				Brain (IH)	CSF ADPN levels were positively correlated with MMSE scores (r = 0.4247, $p < 0.001$) and CSF $A\beta_{42}$ levels (r = 0.1917, $p < .01$) and negatively correlated with severity of medial temporal lobe atrophy (r = −0.2910, $p < .001$) and CSF p-tau levels (r = −0.2979, $p < .001$). There were no correlation between serum ADPN and AD biomarkers

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Table 1 (*continued*)

Study, country of origin	First author, year	n	Age	Sex	Follow-up	ApoE	Cognitive assessment	Sample (method)	Results
MCSA study, USA	Wennberg, 2016	535 NC	80 (77, 84)[a]	328 ♂/207 ♀	0	Yes	MMSE AVLT, WMS-R (LMVR), BNT, Category Fluency, TMT B, WAIS-R (Digit Symbol, Picture Completion, Block Design)	Plasma (RIA)	In men, total ADPN was associated with reduced cerebral glucose uptake (FDG-PET; B = −0.087; 95%CI: −0.166, −0.008) and was **not associated** with odds of MCI In women, higher ADPN levels were associated with smaller hippocampal volume (B = −0.595; 95%CI: −1.19, −0.005) poorer language and global cognitive performance (B = −0.777; 95%CI: −1.42, −0.138 and B = −0.729; 95%CI: −1.40, −0.053, respectively) and with **greater odds** of MCI (OR = 6.23; 95%CI: 1.20, 32.43) Adjustments: age, education, WHR, DM, HT, ApoE, amyloid status

[a] Median (1st, 3rd Quartiles).
[b] Mean ± SD.
[c] Median (Range).

On the other hand, insufficient tools are used in the neuropsychological classification and workout of the patients enrolled. For instance, it is well established that amnesic and non-amnesic MCI carry a different risk of progression to AD but in some of these studies there is no clear distinction between these two conditions. Besides, a great number of studies rely exclusively on Mini Mental State Examination (MMSE) to confirm the diagnosis of cognitive decline (Bigalke et al., 2011; Diniz et al., 2012; Khemka et al., 2014; Kitagawa et al., 2015; Ma et al., 2016; Une et al., 2011; van Himbergen et al., 2012; Waragai et al., 2016) despite the recognized limitations of this instrument to establish AD diagnosis (Chapman et al., 2016). Other potential confounder is the absence of information on AD specific therapy of the patients enrolled, since is not yet clear if acetylcholinesterase inhibitors (AChEI) influence ADPN levels, either directly or indirectly through weight changes, as described below. Several other drugs, such as statins and thiazolidinediones are also prone to affect circulating levels of this protein (Montecucco and Mach, 2009). Furthermore, weight loss, that has been associated with impending cognitive decline and progression to dementia (Cova et al., 2016) may cause, by itself, an elevation in serum ADPN levels, potentially biasing the results of clinical studies.

Analysis of CSF ADPN levels could, in theory, overcome some of the difficulties described and better mirror the influence of this adipokine on AD pathology. Nevertheless, the few clinical studies comparing CSF ADPN levels in cognitively normal controls and in MCI/AD patients reached contradictory conclusions, though none of them differentiated ADPN isoforms or made adjustments based on BBB integrity parameters (Une et al., 2011; Waragai et al., 2016). In fact, though most of the studies have measured ADPN irrespectively of its conformation, this protein has a wide range of multimers that may act differently according to its structure and target cell/tissue, as already mentioned. The pathophysiological relevance of each of these forms remains undetermined mainly due to technical limitations in their detection. In addition, neuroinflammatory changes associated to neurodegeneration can affect BBB integrity and alter its function and permeability to peripheral proteins, and otherwise influence CSF ADPN concentration in these patients (Carvey et al., 2009).

Meanwhile, other pertinent and clinically relevant issue is the extent to which circulating ADPN influences the risk of progression of the disease. The Framingham Heart (van Himbergen et al., 2012), the Washington Heights Inwood Columbia Aging Project (WHICAP II) (Gu et al., 2010) and the Osaka Follow-up Study for Carotid Atherosclerosis (OSACA2) (Kitagawa et al., 2015) are the largest longitudinal studies that have assessed the correlation between baseline adiponectinemia and the risk of progression to MCI or dementia. Despite the large amount of patients included (826, 1219 and 466, respectively) and prolonged periods of follow-up (approximately 13, 4 and 7 years, respectively), only the first study described an increased risk of AD in women with higher plasmatic ADPN concentration (HR = 1.33), while the others reported no association. Considering the results presented by the Framingham Heart Study two opposing hypothesis can be postulated. Either ADPN has detrimental effects and increases the risk of developing the disease, or ADPN is increased in patients that, in spite of asymptomatic, have already neuropathological AD alterations, ADPN is required to counterbalance neurodegeneration. In our opinion, supported by the evidence gathered so far, the last hypothesis seems to be more consistent. In fact, our group has correlated higher CSF ADPN levels in MCI patients with longer time to progression to dementia (unpublished data). Another question raised by this study and others is the difference in results when sex-based subgroup analysis is performed. It is already recognized the existence of a disproportional higher risk for dementia in women (mainly in the oldest-age categories), that is not fully explained by their increased life expectancy (Fratiglioni et al., 1997; Andersen et al., 1999; Chêne et al., 2014). Besides, women with MCI have higher rates of progression (Lin et al., 2015), and those with AD have more severe neuropathology burden (Barnes et al., 2005), experience faster progression of hippocampal

atrophy (Ardekani et al., 2016) and faster rates of cognitive and functional decline after at the diagnosis. (Sinforiani et al., 2010; Tschanz et al., 2011). Several factors seem to contribute to this gender bias: (1) disparities in the educational level and other sociocultural aspects such as lifestyle and behaviors (eg. tobacco and alcohol use); (2) differences in brain development, adult brain structure, function, and biochemistry (Tunç et al., 2016; Köglsberger et al., in press; Djordjevic et al., in press); (3) hormonal factors such as estrogen, progesterone, testosterone, and gonadotropins (Pike, 2017; Lee et al., 2017; Koyama et al., 2016); and (4) inflammatory susceptibility (systemic and microglial) (Podcasy and Epperson, 2016; Mangold et al., 2017). Based in this host of evidence, future studies and clinical trials should consider a deliberate stratification by sex and analyze results and outcomes in men and women separately.

4.2. Adiponectin and AD biomarkers

Pathological features of AD (senile plaques and neurofibrillary tangles) can be reflected in quantifiable biomarkers which constitute useful tools to determine the degree of probability of developing/having the disease. Biomarkers can be divided into different classes based on whether they reflect amyloid beta (Aβ) deposition, such as CSF Aβ and positron emission tomography (PET)-amyloid imaging, or neuronal injury, such as CSF total tau (t-tau) and phosphorylated-tau (p-tau), fluordeoxyglucose-PET (FDG-PET) and volumetric magnetic resonance imaging (MRI) (Albert et al., 2011). For practical reasons, CSF and imaging biomarkers are discussed separately.

4.2.1. CSF biomarkers

Despite growing evidence showing that ADPN may be related to Aβ and tau metabolism, very few studies have evaluated the correlation between ADPN levels and the concentration of these two core CSF AD biomarkers. Waragai et al. (2016) described a weak correlation between CSF ADPN and CSF $A\beta_{42}$ and p-tau ($r = 0.1917$, $p < .01$ and $r = -0.2979$, $p < .001$, respectively) while no correlation was found with serum ADPN. These results support a possible beneficial effect of ADPN once higher CSF levels are associated with lower amyloid and tau burden. However, they must be interpreted with caution because no subgroup analysis based on diagnosis or biomarker profile is presented, ie, all patients (controls, MCI and AD; $n = 189$) were included. More, no reference is made to adjustments for possible confounders such as age, gender, Body Mass Index (BMI) or Apolipoprotein E (ApoE) status. Convergent results regarding the absence of association between serum ADPN levels and CSF $A\beta_{42}$ concentration arise from a small cross-sectional study performed by Diehl-Wiesenecker et al. (2015), which included 30 mild to moderate AD patients.

4.2.2. Imaging biomarkers

Association between ADPN and neuroimaging hallmarks of Alzheimer's type of dementia has also focused researchers' attention. Even though Masaki et al. (2012) described a robust inverse association between serum ADPN levels and hippocampal atrophy, the Mayo Clinic Study Of Aging (MCSA) has recently published opposing data (Wennberg et al., 2016). However, the interpretation of these results must consider that the first study has only enrolled 45 patients (all with type 2 diabetes mellitus and without a thorough cognitive assessment) and in the later study the association between higher serum ADPN and lower hippocampal volume or greater odds of MCI was only significant in a subgroup of women with elevated brain amyloid (assessed by Pittsburgh compound B-PET, PiB-PET). In the same study, higher plasmatic levels of ADPN were associated with reduced cerebral glucose uptake, but only among men. These data suggest that ADPN may only be recruited to the neuroprotective "trenches" when there is excessive amyloid burden or/and impaired glucose metabolism.

García-Casares et al. (2016) has also studied the association between ADPN and voxel based cerebral morphometric parameters in type 2 diabetic patients and described a positive correlation between serum ADPN levels and grey matter density in several regions, including the medial temporal lobe. Our group has assessed for the first time the correlation between CSF ADPN and hippocampal volume in patients with CSF AD print (based on $A\beta_{42}$/p-tau index) with concordant results, ie, patients with low $A\beta_{42}$ and high tau levels presented a strong positive correlation between CSF ADPN and total hippocampal volume (unpublished data).

4.3. The effect of Acetylcholinesterase-Inhibitors on adiponectin levels

Despite discouraging results in the search for disease-modifying treatments for AD, it is already possible to improve the quality of life of these patients and their caregivers through symptomatic treatment. There are currently three AChEI that have been approved by Food and Drug Administration (FDA) for the treatment of AD: Donepezil, the most prescribed drug of its class, which is a centrally acting reversible acetylcholinesterase inhibitor (Shigeta and Homma, 2001), Galantamine, a reversible competitive inhibitor of acetylcholinesterase that also acts as allosteric modulator of nicotinic acetylcholine receptors (Lilienfeld, 2002), and Rivastigmine, an inhibitor of acetylcholinesterase and butyrylcholinesterase (which metabolizes acetylcholine at the synapse, when acetylcholinesterase is loss) (Müller, 2007), all with similar effectiveness (Rafii and Aisen, 2015). These drugs do not alter the course of the disease but instead cause a temporarily improvement in symptoms or slow its worsening.

Currently, there are two studies approaching the effect of AChEI on ADPN circulating levels. Pákáski et al. (2014) has described a linear elevation in serum ADPN levels, as well as a decrease in serum leptin, in AD patients ($n = 26$) after 24 weeks of Donepezil treatment (10 mg/day). A concomitant decrease in the abdominal circumference and BMI are also reported, suggesting that the results may mirror predictable consequences of weight loss rather than a specific adipokine-modifying effect of the drug. Another study conducted by M.A. Ali et al. (2015) depicts an elevation in serum ADPN in type 2 diabetic rats treated with galantamine (2.5, 5 and 10 mg/kg for 4 weeks) associated to weight loss. The drug showed also an insulin-sensitizing effect by acting on the IR/PI3K/Akt/GLUT2 & 4 and Wnt/GSK3β/β-catenin signalling pathways, which in turn could translate an ADPN-related outcome. Additionally, two longitudinal studies enrolling more than 100 AD patients each reported no significant effect of long-term treatment with AChEI intake on patients' body weight (Droogsma et al., 2013; Soysal and Isik, 2016), what is corroborated by the results arising from animal research (Dasuri et al., 2016). Unfortunately, none of these studies have measured the levels of circulating or CSF ADPN or other adipokines, and whether AChEI can influence their concentration, independently of weight changes, is yet to be determined.

4.4. Current state of basic research

Evidence from cellular and animal studies aiming to assess the mechanisms involved in the interaction between ADPN and AD pathophysiological events is listed in Table 2.

Research models have been overall based on cultured hippocampal neuronal cells and wild type or knockout animals treated with ADPN (globular or full-length) with or without a subsequent insult. Its effects on the glia have been, otherwise, much less explored (Wan et al., 2014). Most studies are consistent in assigning to ADPN a neuroprotective role against cytotoxic insults, including Aβ-induced neurotoxicity. Moreover, a couple of studies have reported diminished hippocampal neurogenesis in ADPN-haploinsufficient and/or ADPN-deficient mice, which are reversed with intracerebroventricular (ICV) ADPN administration (Yu et al., 2014; Zhang et al., 2016;). ICV administration has been, indeed, the preferred route to deliver ADPN *in vivo*, once its passage to the CNS remains elusive and high concentrations of the protein have to be administrated peripherally to presumably increment

Table 2
In vitro and animal studies aiming to assess the influence of adiponectin in CNS neuronal and non-neuronal cells involved in cognitive circuits. Aβ: amyloid beta; AD: Alzheimer's Disease; AdipoR: Adiponectin Receptor; ADPN: Adiponectin; AMPK: Adenosine Monophosphate-activated Protein Kinase; APPL1: Adaptor Protein with Phosphotyrosine binding, Pleckstrin homology domains and Leucine zipper motif; BBB: Blood-Brain-Barrier; CNS: Central Nervous System; eNOS: endothelial Nitric Oxide Synthase; ERK: Extracellular signal–Regulated Kinases; fAd: full-lenght adiponectin; gAd: globular Adiponectin; GSK: Glycogen Synthase Kinase; icv: intracerebroventricular; IL: Interleukin; IRS1: Insulin receptor substrate 1; KA: Kainic-Acid; MAPK: Mitogen Activated Protein Kinases; MCP-1: Monocyte Chemoattractant Protein-1; mo: months; NF-kB: Nuclear Factor kappa B; NSCs: Neural Stem Cells; ROS: Reactive Oxygen Species; SH-SY5Y$_{IR}$: Human neuroblastoma cells with insulin resistance; SH-SY5Y$_{swAPP}$: Human neuroblastoma cells expressing Swedish-Amyloid Precursor Protein; VEGF: Vascular Endothelial Growth Factor; w: weeks; WT: wild type. ♂: male.

First author, year (reference)	Cell type (origin) or Animal	Adiponectin (administration)	Treatment	Results
Qiu, 2011	Primary hippocampal neurons (prenatal Sprague Dawley rats)	Recombinant fAd	0.5, 5 and 20 μg/mL for 48 h before insult	ADPN protects neurons against KA induced excitotoxicity *Mechanism:* intracellular ROS and apoptosis reduction, by AMPK signalling pathway activation
Zhang, 2011	Adult hippocampal neural stem cells (Fisher rats)	Recombinant gAd and fAd	0.03–3 μg/ml for 24, 48, 72 h and 6 days	Hippocampal NSCs express AdipoR1and R2; ADPN increases proliferation of adult NSCs but has no effect on apoptosis and differentiation *Mechanism:* activation of the p38MAPK/GSK3β/β-catenin signalling cascade
Chan, 2012	Human neuroblastoma cells SH-SY5Y$_{swAPP}$	Recombinant fAd	10 μg/ml for 2 h before insult	ADPN is protective against Aβ neurotoxicity-induced cytotoxicity under oxidative stress (H_2O_2) *Mechanism:* APPL1-mediated AMPK activation and suppression of NF-kB activation
Wan, 2014	Human astrocytic cells (U373 MG)	Recombinant gAd	1 and 3 μg/mL for 6, 12, 24 and 48 h	Human astrocytes express AdipoR1and R2; gAd exerts pro-inflammatory effects on astrocytic cells *Mechanism:* induction of pro-inflammatory citokine mRNA expression and IL-6 and MCP-1 secretion; ERK1/2, p38 MAPK and NF-kB signalling pathways involved
Song, 2015	Cortical primary NSCs (ICR mice embryos)	Recombinant fAd	30 μg/ml, for 4 days before insult	At high glucose concentrations, ADPN inhibits apoptosis and enhances neurogenesis and proliferation in the NSCs, and restores the reduced expression of AdipoR1 *Mechanism:* p53/p21 activation (apoptosis); via tailless activation
Jeon, 2009	4w ♂ ICR mice	Recombinant fAd (icv)	3 μg/g, 24 h before insult	ADPN pretreatment suppressed KA-induced cell death and VEGF, eNOS and NF-kB expression in the hippocampus as well as BBB permeability
Yu, 2014	8-9w ♂ C57BL/6J mice (WT and ADPN−/−)	Adenovirus expressing ADPN (icv)	2 μg/animal, 2 weeks before behavioral tests	ADPN deficiency diminished the beneficial effects of physical exercise on depression-like behaviors in mice and on hippocampal neurogenesis ADPN treatment reduced depression-like behavior and enhanced hippocampal neurogenesis
Zhang, 2016	9–12w ♂ C57BL/6J mice (WT, ADPN−/− and ADPN−/+)	Recombinant fAd (icv)	1 μg/animal daily, for 7 days	ADPN deficiency decreased dendritic complexity and spine density of dentate gyrus granule neurons and reduced adult hippocampal neurogenesis ADPN treatment increased dendritic spine density and promoted adult hippocampal neurogenesis
Ng, 2016	9 and 18mo ♂ C57BL/6N mice (WT, ADPN−/−) Human neuroblastoma cells (SH-SY5Y$_{IR}$ and SH-SY5Y$_{swAPP}$)	Trimeric ADPN	10 μg/ml	ADPN deficiency increased anxiety levels, impaired spatial learning and memory, and elicited AD-like pathology *Mechanism:* neuronal insulin resistance by inactivating AMPK-IRS1 signalling ADPN treatment enhanced insulin sensitivity in Aβ overproducing cells *Mechanism:* AdipoR1-AMPK activation

its central levels.

Ng et al. (2016) has recently described that chronic ADPN deficiency in aged ADPN-knockout mice lead to AD-like pathology and cognitive deficits, reinforcing the relevance of ADPN in this disease. Nevertheless, studies that modulate circulating ADPN levels in order to determine its effects on cognitive targets are still lacking, and presently we cannot affirm that an elevation of serum ADPN will certainly increment CSF or hippocampal ADPN levels, and consequently its beneficial effects, as some hypothesize to occur in AD patients (Waragai et al., 2016).

4.5. Linking adiponectin and AD signalling pathways

ADPN has been linked to AD-related pathology by several different mechanisms including insulin-sensitizing, anti-inflammatory, anti-apoptotic signalling pathway activation and also by its vascular effects. We summarize below and in Fig.1 the main convergent points along this fat-brain axis.

4.5.1. Insulin

The increased awareness of Diabetes Mellitus (DM) as a risk factor for AD together with the metabolic, molecular and biochemical alterations shared by both diseases culminated in the proposal of the term “type 3 diabetes” to designate sporadic AD. AD is characterized by cerebral glucose dysmetabolism that includes the development of insufficiency and/or resistance to insulin and insulin-like growth factor (IGF) actions on neuronal survival and cognitive processes (De Felice FG et al., 2014; de la Monte and Wands JR, 2008). Several studies have highlighted the overlap between insulin resistance and amyloidogenic pathways (Blázquez et al., 2014; Chami et al., 2016; de la Monte, 2009; Zhao and Townsend, 2009). Amyloid plaques are neuropathological hallmarks of AD representing extracellular neurotoxic deposits, mainly composed by Aβ peptides, which result from aberrant degradation of APP and/or insufficient clearance of its insoluble aggregates. There is a bidirectional relation between insulin and Aβ. Aβ accumulation promotes downregulation of membrane insulin receptor (IR) and inhibition of IR tyrosine kinase signalling while insulin increases amyloidogenic Aβ production (triggering glycogen synthase kinase: GSK3α-dependent APP γ-secretase activity) and impedes Aβ transport and clearance (mediated by insulin-degrading enzyme: IDE, lipoprotein receptor protein: LRP and α2-macroglobulin) (Zhao and Townsend, 2009). Additionally, impairment of IR function results in increased activity of GSK3β, since IR activation inhibits this kinase via PI3K/Akt, which leads to enhanced tau phosphorylation and consequently, promotes neurofibrillary tangle formation, another neuropathological hallmark of AD (El Khoury et al., 2014). Similarly, ADPN and insulin signalling pathways have multiple interactions. Briefly, in the liver, ADPN inhibits glucose production and upregulates insulin receptor substrate 2 (IRS-2), while in skeletal muscle it increases glucose uptake (promoting GLUT4 translocation to plasma membrane) and ameliorates oxidative status. ADPN also indirectly augments insulin sensitivity by inducing fatty acid oxidation, and thus reduces free fatty acids (FFA) and ectopic lipid deposition. In addition, it potentiates insulin secretion by acting directly on pancreatic β cells, increasing insulin gene expression and regulation of local cell apoptosis and proliferation. As an anti-inflammatory adipokine, it may also improve general insulin sensitivity by reducing adipose tissue inflammation (Cheng et al., 2014). Overall, ADPN modulates peripheral (and likely also central) insulin resistance and may indirectly alleviate β-amyloid and p-tau burden.

4.5.2. Inflammation

The relevance of neuroinflammation in AD has been supported by a great amount of evidence that highlights the contribution of inflammatory mediators to disease progression (Heneka et al., 2015; Morales et al., 2014). Moreover, the identification of susceptibility genes for the development of AD which are concomitantly genes coding for immune receptors (eg. TREM2) further consolidated this association (Jonsson et al., 2012). Astroglia and microglia are the major sources of pro-inflammatory molecules in the CNS while simultaneously responsible for immunological surveillance and synaptic remodelling (Furman et al., 2012; Ji et al., 2013). Microglia can be activated by pathological neuronal death or Aβ aggregates promoting its clearance and restoring homeostasis. However, external factors, such as systemic inflammation and obesity, may affect this physiological innate immune response that becomes detrimental if sustained or exaggerated (Heneka et al., 2015). Overall, it is recognized that peripheral inflammatory dysregulation can drive neuroinflammation by promoting sustained glial activation (especially if microglia is already primed as is the case in AD) and consequently cause functional and structural changes that will culminate in neurodegeneration (Heneka et al., 2015).

Dysfunctional adipose tissue is an important source of peripheral pro-inflammatory mediators as it is characterized by a systemic chronic low-grade inflammatory status (Gómez-Hernández et al., 2016) that is concomitantly cause and consequence of lower ADPN circulating levels in obese individuals (Fig.1). It is generally accepted that ADPN is a systemic anti-inflammatory adipokine, capable of macrophage polarization towards an anti-inflammatory M2 phenotype by inhibiting tumor necrosis factor (TNF) α, INFγ, monocyte chemoattractant protein 1 (MCP-1) and IL-6 production as well as increasing anti-inflammatory citokine production (eg IL-10, IL-1Ra) (Turer and Scherer, 2012), and thus could be able to counterbalance neuroinflammation.

4.5.3. Apoptosis

Severe neuronal loss is a constant feature of AD (Serrano-Pozo et al., 2011). However, the underlying mechanisms leading to neuronal cell death are uncertain. Apoptotic signalling pathways are upregulated in AD (Shafi, 2016), though other mechanisms such as autophagic cell death, excitotoxicity, necrosis (Gorman, 2008) and necroptosis (Caccamo et al., in press) are also involved.

An anti-apoptotic role is also assigned to ADPN and carried out by the activation of the enzyme ceramidase and consequently the enhancement of its metabolite, sphingosine-1-phosphate (S1p) (Holland et al., 2011). S1p is a bioactive sphingolipid derived from sphingosine, which is phosphorylated by 2 sphingosine-kinases (SphK1 and 2), and is involved in survival pathways (Cuvillier et al., 1996). It is a potent neuroprotective factor against soluble Aβ-induced apoptosis (Malaplate-Armand et al., 2006) and promotor of long-term potentiation, which is essential to memory consolidation (Kanno et al., 2010). But the relation with AD pathophysiology goes even further. In hippocampus and temporal cortex, decreased levels of S1p have been associated with higher Braak stage, ie, with higher neurofibrillary tangle (NFT) burden. Interestingly, ApoE regulates the secretion of S1p, and hippocampal S1p/sphingosine ratio is higher in ApoEe2 carriers compared to ApoEe4 carriers, linking this sphingolipid to the most relevant genetic risk factor for late onset AD (Couttas et al., 2014). Thus, S1p constitutes one more possible convergent molecule in ADPN and AD metabolisms, that further supports its role in neuroprotection.

4.5.4. Macro- and microangiopathy

Cerebrovascular dysregulation is thought to be an early event in AD and contribute to its progression. Several researchers defend a vascular etiology for Alzheimer’s disease (de la Torre, 2002) and substantial body of evidence suggests that neurodegeneration can be initiated by chronic cerebral hypoperfusion and dysregulation of cerebral blood flow associated with aging or other classical vascular risk factors such as obesity (Di Marco et al., 2015b). In fact, it seems to exist a vicious circle linking Aβ and vascular impairment, in which Aβ reduces endothelial nitric oxide synthase (eNOS) synthesis, upregulates endothelin-1 and induces calcium homeostasis impairment promoting, in association with the cholinergic deficit, alterations in cerebrovascular reactivity and vasomotion (spontaneous rhythmic modulation of arterial diameter). This will, in turn, affect the clearance of perivascular

Aβ and other neurotoxic substances and enhance oxidative stress (Di Marco et al., 2015a) contributing to AD progression. AdipoRs are expressed in brain vascular endothelial cells and their role as anti-atherogenic and anti-hypertensive agents have been well established, though most of the evidence come from cardiovascular studies. Not surprisingly, low circulating ADPN levels have been consistently associated with atherosclerotic cerebrovascular disease and increased mortality after ischemic stroke (Chen et al., 2005; Prugger et al., 2012). Moreover, ADPN modulates the expression of endothelial adhesion molecules (Ouchi et al., 1999, 2000), stimulates eNOS phosphorylation and nitric oxide (NO) production (Chen et al., 2003; Nishimura et al., 2008) and regulates angiogenesis (Ouchi et al., 2004; Shibata et al., 2004) potentially protecting the brain against β–induced vascular impairment.

4.6. Direct effects of adiponectin on neuronal and glial cells

It has been demonstrated that beyond the indirect effects on the pathological cascade of events described above, ADPN stimulates neural stem cell proliferation (Song et al., 2015; Zhang et al., 2011) and may also be considered a neuroprotective agent by acting directly in neuronal and glial cells. Several models of neuronal toxicity support this hypothesis (see Table 2). Jeon et al. (2009) and Qiu et al. (2011) were the first to demonstrate the neuroprotective effects of ADPN in a kainaic acid-induced excitotoxic model. Subsequent studies using APP transfected-neuroblastoma cells and ADPN-knockout mice models further corroborated that ADPN is protective against Aβ neurotoxicity, demonstrating that chronic ADPN deficiency induces AD-like pathology (including microglial activation and astrogliosis) as well as cognitive impairment (Chan et al., 2012; Ng et al., 2016). The molecular mechanisms involved include mostly AdipoR1/phosphotyrosine and its interaction with PH domain and leucine zipper 1: APPL1/AMPK (Chan et al., 2012; Jeon et al., 2009; Qiu et al., 2011) and also AdipoR1/APPL1/IRS1/2 downstream signalling events (Ng et al., 2016). These results are reinforced by two recent studies that demonstrate that osmotin, a natural homolog of ADPN, counteracts amyloidogenic Aβ production and aggregation, tau hyperphosphorylation, synaptic dysfunction and hippocampal neurodegeneration through the regulation of PI3K/Akt/GSK3β (Ali et al., 2015) and/or AMPK/SIRT1 (Shah et al., 2016) signalling pathways.

Remarkably, AD brain neuropathological data, though still very limited, favors the existence of a direct interaction between ADPN and the histological hallmarks of AD (Vingtdeux et al., 2011; Waragai et al., 2016). It suggests that this adipokine can have a buffering effect on the aggregates' neurotoxicity, which may be mediated by AMPK, once ADPN co-localizes with NFTs in AD brains (Waragai et al., 2016) and AMPK accumulates around amyloid plaques of neurons bearing NFTs (Vingtdeux et al., 2011).

Beyond the recognized peripheral regulation of inflammation by ADPN, its effects on microglia and astrocytes are almost unexplored. Chabry et al. (2015) showed that icv ADPN has potent anti-inflammatory effects on microglia of corticosterone-treated mice, by reducing the level and expression of pro-inflammatory genes (IL-1β, IL-6, TNFα, inhibitor of kappa-light-chain-enhancer of activated B cells: IκB-α) and increasing mRNAs of anti-inflammatory mediators (Arg1, IL-10). To our knowledge there is only one study that has determined the effect of gAd on astrocytic cells with results indicating a pro-inflammatory effect involving IL-6, MCP-1, IL-1β and IL-8 (Wan et al., 2014). Further investigation is imperative to understand the impact of ADPN on CNS inflammation, taking into account that inflammation may be beneficial in the earliest phases of AD (Chakrabarty et al., 2010, 2012).

5. Adiponectin as a potential therapeutic target in AD

Based on recently published data from cellular, animal and clinical studies, it is reasonable to speculate that ADPN can be considered a molecule of interest in the search for new neuroprotective targets for AD. Besides lifestyle modifications (such as diet and physical exercise) and bariatric surgery, which are able to increase ADPN secretion (independently of weight loss), there is growing interest in pharmacological strategies that target ADPN, AdipoR or its downstream signalling pathways.

Several drugs have shown their ability to increase plasma ADPN levels (Montecucco and Mach, 2009), and presumably, its cerebral levels. Some examples include Statins, Angiotensin II Receptor Blockers, Angiotensin-converting Enzyme Inhibitors, Peroxisome proliferator-activated receptors: PPAR-γ Agonists (thiazolidinediones), Fibrates and Cannabinoid Type 1 Receptor Blockers, that have otherwise been also associated with neuroprotective pleiotropic effects, although none of these drugs are currently approved for AD (Cheng et al., 2016; Dufouil et al., 2005; Fakhfouri et al., 2012; Mcguinness et al., 2016; O'Caoimh et al., 2014; Zhou et al., 2016).

Direct peripheral administration of ADPN (intravenous or intraperitoneal), though representing the most obvious replacement strategy, has important limitations. These include: its high concentration in plasma (μg/mL) with the need of high dosis administration, the existence of different isoforms with unclear action/site of action, elevated costs and possible feedback loops in which ADPN downregulates its own production and AdipoR expression (though only demonstrated for AdipoR2). Similar to leptin and insulin, ADPN peripheral resistance has also been described and may represent a major obstacle to its peripheral administration (Sun et al., 2009). Central resistance to leptin and insulin are likewise described in obesity and AD, but whether the same occurs with ADPN remains unexplored. If ADPN could be delivered to the CNS, some of the limitations described above would be overridden, including the amount of protein required. Various non-invasive methods, such as drug lipophilic transformation, prodrugs and intranasal drug delivery are already widely used in neurodegenerative diseases research. Intranasal gAd treatment has already been used in mice models of a-synucleinopathies with beneficial effects in disease progression (Sekiyama et al., 2014). However, the utilization of AdipoR agonists has been suggested as the most promising therapeutic approach (Okada-Iwabu et al., 2013; Kadowaki et al., 2014), though specific molecular key mediators in the ADPN signalling pathway, such as APPL1, may also be suitable candidates in the search for therapeutic targets.

As more accessible alternatives, natural products have been studied as anti-neurodegeneration agents. The most paradigmatic example is osmotin, that is present in fruits and vegetables, and may act as an AdipoR agonist and whose beneficial effects in AD-like pathology were described in Section 4.6.

6. Conclusion and future directions

Current research indicates that ADPN affects, directly or indirectly, the risk of developing AD and also its progression. However, further investigation is required in order to clarify how peripheral concentrations of this adipokine can modulate its central effects, as well as the exact functions and receptor-dependent or independent downstream pathways activated by each isoform. This will, in our opinion, facilitate data interpretation and enhance congruency of the results delivered by clinical research. Ultimately, a thorough understanding of ADPN physiology, especially its actions on the hippocampus and cerebral cortex will hopefully shed light on some (still) unanswered questions such as why is mid-life obesity a risk factor for late-onset AD or why is peripheral ADPN elevated in AD patients.

Conflicts of interest

None.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

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