MINIREVIEW

# Adiponectin and Alzheimer's disease: Is there a link?

Zhongxiao Wan, Jonathan P. Little

*School of Health and Exercise Sciences, University of British Columbia Okanagan, Kelowna, British Columbia V1V 1V7, Canada*

Correspondence: Jonathan P. Little
E-mail: jonathan.little@ubc.ca
Received: April 14, 2014
Published online: November 14, 2014

**Obesity is a recently established risk factor for Alzheimer's disease (AD) and dementia. The mechanisms linking obesity to AD have not been firmly established and therefore no evidence-based hypotheses exist for designing preventative or therapeutic interventions. Adiponectin is the most abundant adipokine in the circulation and its levels are substantially reduced in obesity. In peripheral tissues, adiponectin exerts a wide range of beneficial physiological actions, including anti-diabetic, anti-inflammatory, anti-atherosclerotic and cardioprotective effects. Several different lines of evidence indicate that adiponectin exerts effects on the brain, but data is still conflicting. Recently work from our laboratory confirmed the expression of adipoR1 and adipoR2 in primary human astrocytes isolated from adult brain samples and we found that globular adiponectin induced astrocyte inflammation. Due to the prominent role of brain inflammation in AD, astrocyte inflammation induced by globular adiponectin could be involved in AD-related pathology. In this brief review, we summarized the evidence connecting obesity and AD, with a specific focus on the potential involvement of adiponectin. We also suggest approaches for further exploring adiponectin's effects in AD pathogenesis. Elucidating the role of adiponectin in AD-related pathology will hold promise for identifying potential therapeutics that could promote positive effects of adiponectin for the prevention and/or treatment of AD and dementia in the context of obesity.**

***Keywords:*** adipokines; astrocytes; dementia; obesity; high fat diet; neuroinflammation

**Abbreviations:** AD, Alzheimer's disease; NFTs, neurofibrillary tangles; Aβ, amyloid beta; T2DM, type 2 diabetes; TZDs, thiazolidinediones; PUFAs, poly-unsaturated fatty acids; adipoR1, adiponectin receptor 1; gAd, globular adiponectin ; NFκB, nuclear factor kappa B; MAPK, mitogen-activated protein kinase; JNK, c-Jun N-terminal kinase; PI3K, phosphatidylinositide 3-kinase ; ERK, extracellular signal-related kinase; KO, knockout; ATCM, Adipose tissue conditioned media; ATOC, Adipose tissue organ culture.

**To cite this article:** Wang Z, *et al*. Adiponectin and Alzheimer's disease: Is there a link? Inflamm Cell Signal 2014; 1: e154. doi: 10.14800/ics.154.

## 1. Introduction

Alzheimer's disease (AD) is characterized by progressive cognitive decline, loss of memory, and dementia, and is the most common neurodegenerative disease in humans. The pathological hallmarks of the disease are neurofibrillary tangles (NFTs) comprised of hyperphosphorylated tau[1] and senile plaques comprised of amyloid beta (Aβ)[2], which result in neuronal death and dysfunction. A significant inflammatory component is also present in brains of individuals with AD, consisting of activated microglia and astrocytes and an increase in levels of brain cytokines[3-4].The disclosure of AD presents a great challenge because it not only affects patients' quality of life but also has significant impact on family members and caregivers. At present, neither a satisfying therapy nor a preventative cure is available for AD. This is largely because our knowledge of the complex biology of AD is incomplete, highlighting the importance of exploring and

understanding new mechanisms underlying AD progression.

## 2. Obesity and increased risk of AD

The most significant risk factor for AD is aging but mounting evidence now suggest that obesity represents an independent risk factor for AD and related dementias[5-7]. Research linking obesity to AD can be summarized as follows: 1) Longitudinal studies report that overweight, obesity, and/or increased abdominal adiposity in mid-life result in ~1.5 to 3-fold greater risk of developing AD, dementia or cognitive impairment later in life[5-6, 8-10]; 2) Many consequences of obesity-including impaired glucose tolerance, type 2 diabetes (T2DM), and cardiovascular disease-are also risk factors for AD[11-15]. Increased risk of AD in obesity and T2DM is separate from vascular dementia and appears to persist after adjustment for cardiovascular risk factors such as stroke, hypertension, and cerebrovascular disease, suggesting an independent role for obesity-related metabolic dysfunction; 3) High-fat feeding, which is used to model obesity, results in impaired cognitive function in rodents[16-17] and humans[18], as well as increased astrogliosis[19-21], and microglial activation[17; 19-21] in rodent brains; 4) A recent review using population attributable risk scores estimated that 7% of all AD cases in the USA can be attributed to midlife obesity[22]. Despite this mounting evidence supporting the association between obesity and increased risk of AD, the mechanistic links between obesity and AD brain pathology remain incompletely understood.

## 3. Adiponectin: a potential mechanistic link between obesity and AD?

### 3.1 Evidence gleaned from adiponectin action in peripheral tissues

It is now well-accepted that adipose tissue is an active endocrine organ that secretes a host of hormone-like substances termed "adipokines"[23]. Adipose tissue contains adipocytes, preadipocytes, endothelial cells, and various immune cells and thus adipokines may originate from any one of these diverse cell types. Adiponectin, the most abundant adipokine in circulation, is thought to be secreted almost exclusively by adipocytes[24]. Several experimental and clinical studies have shown that adiponectin is inversely related with adiposity, resulting in lower circulating levels of adiponectin in obesity [25-26]. In peripheral tissues, adiponectin improves insulin sensitivity[27-28] and vascular function[29], and has anti-atherogenic, anti-inflammatory actions[30] and cardioprotective effects[31]. Thus, reduced adiponectin in obesity could indirectly influence AD risk through modulation of several interrelated systemic factors. However, emerging, yet currently incomplete, evidence suggests that adiponectin may impact AD risk through direct effects in the brain.

### 3.2 Potential beneficial effects of adiponectin in the central nervous system (CNS)

Adiponectin receptors are widely distributed in the CNS[32-34]. Recent studies show that circulating adiponectin enters the brain fluid from the circulation, and the trimer and hexamer forms of adiponectin can be detected in the cerebrospinal fluid[35-38]. Lee *et al*.[39] reported that adiponectin knockout (KO) mice have enhanced kainic acid-induced seizure severity, but only when animals are rendered obese through high-fat feeding. This provided the first evidence suggesting that adiponectin could link obesity-related metabolic dysfunction to greater risk of neurodegeneration. Substantial associative evidence also supports a neuroprotective effect of adiponectin, including: 1) Clinical and animal studies report that thiazolidinediones (TZDs) and omega-n-3 poly-unsaturated fatty acids (PUFAs) have benefits on cognitive impairment associated with dementia and AD[40-42]. An increase in plasma adiponectin is one of the most notable and common responses to TZDs treatment and n-3 PUFAs supplementation [41-42]. Thus, adiponectin might play a role in TZD's and n-3 PUFAs' beneficial effects on the brain. 2) Insulin resistance is another significant risk factor for AD[5, 43]. Longitudinal studies show that insulin resistance is associated with increased risk of AD[44-45], increased amyloid Aβ plaques and NFTs[43] and hippocampal atrophy[46]. Adiponectin is a well-known insulin sensitizer[27-28]. By enhancing insulin sensitivity, adiponectin might reduce brain pathology and AD risk. Furthermore, at the cellular level, Chan *et al*.[33] reported that high concentrations of adiponectin (10 μg/ml) were protective against amyloid beta induced neurotoxicity in Sw-APP transfected SH-SY5Y cells exposed to oxidative stress conditions, further supporting adiponectin might be protective against AD.

### 3.3 Potential detrimental effects ofadiponectin in the CNS

In contrast to the above mentioned benefits of adiponectin on AD risk there is also evidence supporting a detrimental effect of adiponectin with regards to neurodegeneration. The Framingham Heart Study showed that individuals with higher levels of adiponectin had increased risk of future dementia[47]. Une *et al*. [48] have also reported elevated cerebrospinal fluid adiponectin in older adults with mild cognitive impairment compared to healthy age-matched individuals, suggesting that elevated CNS adiponectin tracks AD risk. A pathogenic role for adiponectin has also been described in ischemic stroke, where adiponectin receptor 1 (adipoR1) expression is increased and globular adiponectin (gAd) enhances neuronal cell death in response to glucose and oxygen deprivation[49]. Recently, work from our laboratory

confirmed the expression of adipoR1 and adipoR2 in primary human astrocytes isolated from adult brain samples and we found that gAd induced astrocyte inflammation[34]. Based on pharmacological inhibitor experiments, the induction of inflammatory cytokine production in astrocytes appeared mediated by several classical inflammatory pathways, including nuclear factor kappa B (NFκB), p38 mitogen-activated protein kinase (MAPK), c-Jun N-terminal kinase (JNK), phosphatidylinositide 3-kinase (PI3K), and particularly extracellular signal-related kinase (ERK) 1/2[34]. Thus, augmented brain inflammation may be a potential cellular mechanism linking adiponectin with the previously described neurodegenerative consequences[34]. Further studies are warranted to examine the impact of adiponectin on brain function in neurodegenerative disorders including AD. One physiological complication in studies of adiponectin and dementia is the association with energy balance. Adiponectin tends to increase in conditions of negative energy balance (i.e., weight loss) yet weight loss has been shown to be a significant predictor of impending dementia[50-51]. Therefore, in studies showing an association between increased adiponectin and cognitive impairment[47,48] it is possible that negative energy balance was a confounding factor.

### 3.4 Potential approaches to further explore the action of adiponectin in the pathogenesis of AD

*1) Adiponectin knockout (KO) mice*

Multiple strains of adiponectin KO mice have been created in different laboratories[52-55]. Although phenotypes are somewhat variable, generally adiponectin KO mice (6-16 wks of age) show only subtle changes in metabolic phenotype when fed a chow diet, e.g. slight insulin resistance compared to WT mice[52, 55] or normal insulin sensitivity[53], and no difference in body weight and food intake[54]. In response to HFD (≥2 wks), adiponectin KO mice display markedly greater fat mass, insulin resistance, glucose intolerance, and chronic inflammatory markers compared to WT littermates[52, 54-55]. A recent study reported that adiponectin KO mice developed marked fibrosingsteatohepatitis 40 wks after HFD[56]. It would be interesting to explore whether adiponectin KO mice will develop more AD related pathology under chow and HFD conditions compared to age matched WT control.

*2) Commercially available adiponectin peptides for in vitro or infusion studies*

Adiponectin exists in different conformations including trimer, hexamer and high-molecular weight forms[57] as well as a globular isoform, which is produced after proteolytic cleavage of full-length adiponectin monomers by neutrophil elastase[58]. Different isoforms of adiponectin have been shown to play distinct biological roles in peripheral tissues[59-60]. Our recently published data suggest that globular adiponectin (1μg/ml) induces a pro-inflammatory state in human astrocytic U373 MG cell line[34], which is in consistent with the findings about globular adiponectin in peripheral tissues[61-62]. This data suggesting a link between globular adiponectin and AD-related brain pathology (i.e., inflammation) is consistent with studies reporting that globular adiponectin enhances neuronal death under hypoxic conditions[49]. The roles played by other forms of adiponectin in neuroinflammation and neurodegeneration require further exploration. Future cellular research is also needed to study potential interactions between the different forms of adiponectin and other established signaling molecules in AD-related pathology.

*3) Adipose tissue conditioned media (ATCM): a model of adipose-brain crosstalk?*

Adiponectin is one of the most abundant proteins in serum, circulating in the μg/ml range. The physiological levels of adiponectin in human cerebrospinal fluid are reported to be ~1000-fold less than in serum[63]. It is of importance to explore how adiponectin, at physiological levels, exert its action in the CNS, as well as determining the function of adiponectin in combination with other adipokines. In this regard, human adipose tissue conditioned media provides a unique way to explore potential adipose-brain crosstalk. Adipose tissue organ culture (ATOC) is a well-recognized technique to study adipose tissue function that maintains the complex interplay of cells that is representative of normal physiology [64]. ATOC is a relatively easy technique and cultures can be prepared from surgical or biopsy samples[64] from different adipose tissue depots. ATCM can be stored at -80°C and further utilized for transferring to different cell lines (such as neuronal or glial cell cultures). This technique allows the paracrine and/or autocrine interactions between adipocytes and other cell types in adipose tissue to remain intact and is arguably more representative of what is seen *in vivo* compared to isolated adipocyte preparations. Thus, altered adipokine secretion from subjects with different metabolic status (such as lean vs. obese, and non-T2DM vs. T2DM) can be prepared and ATCM can be used to treat brain cell cultures to study how physiological combinations of adipokines impact mechanisms of neurodegeneration. Because adipose tissue remains buoyant and floats during ATOC procedures, direct co-culture of adipose with adherent brain cell lines can also be performed with, or without, the use of tissue culture inserts. These techniques will be potentially useful for exploring whether altered adipose tissue secreted factors (especially decreased adiponectin secretion) owing to different metabolic status are involved in the pathogenesis of AD. Because depot-specific differences in adipose tissue remain during the culture procedure [65], this approach will be

potentially helpful for determining whether fat from different depots might have different roles in AD pathology.

## 4. Final remarks

Given the alarming rates of obesity worldwide, understanding the mechanisms underlying the increased risk of AD in obesity is essential to develop evidence-based therapies for mitigating AD risk. Adiponectin may act locally or systemically, influencing numoerous biological processes including energy metabolism, insulin sensitivity, vascular function, neuroendocrine function and immune responses. Several different lines of evidence, from longitudinal cohort studies in humans[47] to mechanistic studies in cell culture[33-34] indicate that adiponectin exerts effects on the brain, but data is still conflicting and further studies are needed to clarify the precise actions of adiponectin in the CNS. Elucidating the role of adiponectin in AD-related pathology will hold promise for identifying potential therapeutics (e.g. pharmacological induction of adiponectin, targeted lifestyle strategies) that could promote positive effects of adiponectin for the prevention and/or treatment of AD and dementia in the context of obesity.

## Conflicting Interests

The authors declare they have no conflicting interests.

## Acknowledgements

Work in the corresponding author's laboratory is supported by a Natural Sciences and Engineering Research Council (NSERC) of Canada Discovery Grant. ZW is supported by an Alzheimer's Society Research Program (ASRP) Postdoctoral Fellowship.

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