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: June 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


Copyright: © 2014 The Authors. Licensed under a Creative Commons Attribution 4.0 International License which allows users including authors of articles to copy and redistribute the material in any medium or format, in addition to remix, transform, and build upon the material for any purpose, even commercially, as long as the author and original source are properly cited or credited.

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 suggests 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 antiatherogenic, 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-3 polyunsaturated 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\(^{[15, 43]}\). 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 of adiponectin 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 (NFkB), p38 mitogen-activated protein kinase (MAPK), c-....

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, exerts 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 coculture 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 numerous 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 to mechanistic studies in cell culture, 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.

References


53. Ma K, Cabrero A, Saha PK, Koijima H, Li L, Chang BH, et al. Increased beta-oxidation but no insulin resistance or


