Review Article
http://dx.doi.org/10.5115/acb.2013.46.4.229
pISSN 2093-3665 eISSN 2093-3673
Anatomy & Cell Biology acb

Adiponectin as a new paradigm for approaching Alzheimer's disease

Juhyun Song[1], Jong Eun Lee[1,2]
[1]Department of Anatomy, Yonsei University College of Medicine, [2]BK21 Plus Project for Medical Sciences, Yonsei University College of Medicine, Seoul, Korea

Abstract: Adiponectin is an adipocytokine released by the adipose tissue and has multiple roles in the immune system and in the metabolic syndromes such as cardiovascular disease, Type 2 diabetes, obesity and also in the neurodegenerative disorders including Alzheimer's disease. Adiponectin regulates the sensitivity of insulin, fatty acid catabolism, glucose homeostasis and anti-inflammatory system through various mechanisms. Previous studies demonstrated that adiponectin modulates memory and cognitive impairment and contributes to the deregulated glucose metabolism and mitochondrial dysfunction observed in Alzheimer's disease. Here, we aim to summarize recent studies that suggest the potential correlation between adiponectin and Alzheimer's disease.

Key words: Adiponectin, Alzheimer's disease, Brain insulin system, Cognitive impairment

Received October 23, 2013; Revised November 6, 2013; Accepted November 13, 2013

Introduction

Adiponectin is a protein hormone and an adipocytokine released by the adipose tissue. Adiponectin has an N-terminal collagen-like domain and a C-terminal complement factor C1q-like globular domain and circulates as trimers, hexamers, and a high molecular weight form. Adiponectin acts by binding to its receptors, adiponectin receptor type 1 and type 2. Adiponectin receptors are expressed in skeletal muscle, liver, hypothalamus and vascular endothelial cells of brain [1-3]. Adiponectin has important roles in the metabolic syndromes such as obesity, cardiovascular disease, type 2 diabetes and also neurodegenerative disorders [4-11]. In the central nervous system (CNS), previous studies suggest the neuroprotective effects of adiponectin [12, 13]. Adiponectin was shown to be present in the cerebrospinal fluid of rodents [14, 15] and human [16-19]. In addition, adiponectin modulates the sensitivity of insulin in brain [20-22]. Also, adiponectin has a cardinal role in immune system in the CNS. Adiponectin decreases the expression of pro-inflammatory cytokines [23] and increases the expression of anti-inflammatory molecules [24]. To sum up, adiponectin has important functions as a regulator of glucose homeostasis and insulin mechanism and immune system. Therefore, adiponectin suggested as a potential target to cure CNS diseases.

The Effect of Adiponectin on Brain Insulin System

Insulin plays multiple roles for neuronal function and survival. In Alzheimer's disease brain, level of insulin and insulin like growth factor-1 (IGF-1) decreases definitely compared to normal brain [25, 26]. Both the expression and function of insulin and IGF-1 deteriorate with progression of Alzheimer's disease [27]. Adiponectin-mediated activation of AMP-activated protein kinase, the p38 mitogen-acti-

Corresponding author:
Jong Eun Lee
Department of Anatomy, Yonsei University College of Medicine, Brain Korea 21 Project for Medical Science, Yonsei University, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Korea
Tel: +82-2-2228-1646, 1659, Fax: +82-2-365-0700, E-mail: jelee@yuhs.ac

Copyright © 2013. Anatomy & Cell Biology

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

vated protein kinase and Rab5 leads to increased glucose transporter 4 membrane translocation [28, 29]. Adiponectin modulates the sensitivity of insulin, glucose metabolism [20-22]. In rodents, the deletion of adiponectin gene leads to insulin resistance [30, 31]. In humans, a reduced serum concentration of adiponectin incurs obesity, insulin resistance and type 2 diabetes [32-34]. Impaired proximal signaling of insulin receptor also mediates insulin resistance. Decreased insulin receptor substrate (IRS) protein levels contribute insulin resistance in rodents and humans [35]. The IRS protein levels decrease in streptozotocin induced dementia rat model which have used to study Alzheimer's disease as animal model compared with sham group (normal control group) in the hippocampus (Fig. 1A) and in the cortex (Fig. 1B). In Alzheimer's disease, insulin system dysfunction incurs severe pathology such as cognitive decline suggesting that adiponectin could be an important target for Alzheimer's disease.

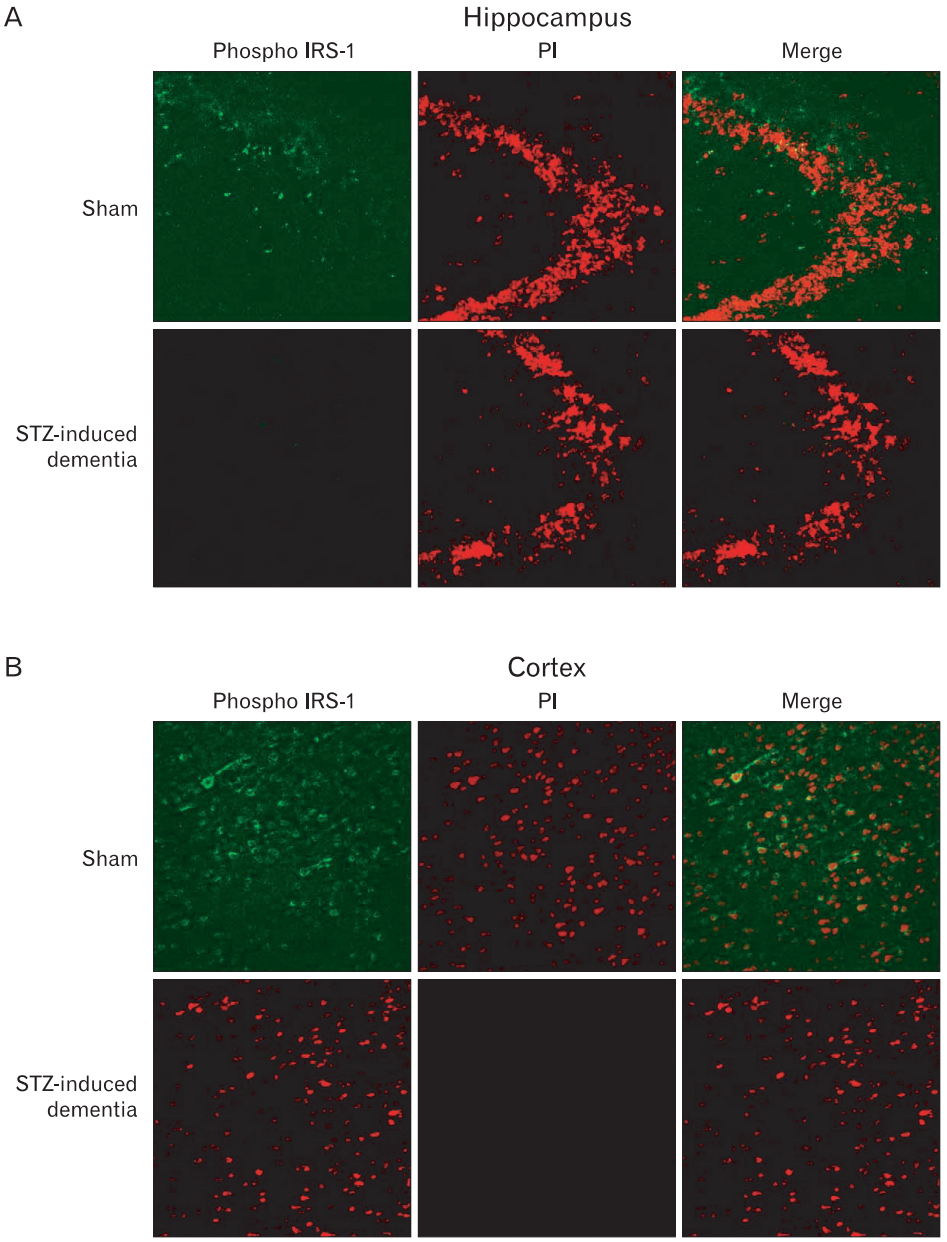

Fig. 1. The phospholylation of insulin receptor substrate (IRS)-1 in streptozotocin (STZ) induced dementia rat model. To confirm the dysfunction of brain insulin system in STZ—induced dementia rat model known as common animal model to study Alzheimer's disease *in vivo*, we conducted immunohistochemistry using phospho IRS-1 antibody. (A) In the hippocampus, phospholylation of IRS-1 decreased in the STZ induced dementia group compared with sham (control group). (B) In the cortex, phospholylation of IRS-1 decreased in the STZ induced dementia group compared with sham (control group). Green color, phospho IRS-1; red color, propidium iodide (PI).

The Role of Adiponectin on Neuroinflammation

Adiponectin has a cardinal role in immune system in CNS. Adiponectin is the most abundant anti-inflammatory adipokine and decreases the expression of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) [23] and increases the expression of anti-inflammatory molecules such as interleukin (IL)-10, IL-1 receptor antagonist [24] and decreases the activation of the pro-inflammatory signal pathway such as nuclear factor-κB pathway [21, 23]. In the brain endothelial cell, adiponectin reduces secretion of IL-6 as a pro-inflammatory cytokine [6]. As pro-inflammatory factors such as TNF-α, IL-6, reactive oxygen species suppress the expression of adiponectin in adipocytes, adiponectin levels are decreased in obese rodents and humans [36]. In addition, adiponectin modulates T cells activation. Adiponectin receptors are upregulated on the surface of human T cells after antigen stimulation and mediate apoptosis of antigen specific T cells resulting in the suppression of antigen specific T cells expansion [37]. Also, adiponectin modulates the inflammatory function of natural killer cells [38]. Visceral adipose tissue is positively associated with risk of insulin resistance and shows higher monocytes infiltration and IL-6 production than subcutaneous adipose tissue [39, 40]. TNF-α also induces serine phosphorylation of IRS1 to modulate the downstream effectors of the insulin receptor resulting in insulin resistance [41]. Th_{17} $CD4^+$ T cells are not involved in the inflammation of obese mice [42]. Cytotoxic $CD8^+$ T cells are significantly increased in adipose tissues of obese mice, and depletion of $CD8^+$ T cells reverses inflammation and insulin resistance suggesting that obesity-induced infiltration of $CD8^+$ T cells deteriorate systemic insulin sensitivity [43]. Various immune responses relate with brain insulin resistance and adiponectin involves the relationship between immune responses and insulin resistance. Collectively, adiponectin has multiple roles in immune system and affects brain insulin system. Hence, adiponectin may be a promising target for curing Alzheimer's disease which associates with inflammation and insulin resistance.

The Potential of Adiponectin to Target Alzheimer's Disease

Adiponectin modulates brain metabolism and sensitivity of insulin [1, 44] regulating memory and cognitive dysfunction [45] and it also regulates severe inflammaion observed in mild cognitive impairment and Alzheimer's disease [46-48]. In particular, adiponectin contributes to the deregulated glucose metabolism and mitochondrial dysfunction observed in Alzheimer's disease [49, 50]. Specifically, adiponectin increase in blood insulin, not glucose level in Alzheimer's disease [51]. Insulin dysregulation contribute to Alzheimer's disease pathologies by several mechanisms from reduced brain gulcose utilization to neurofibrillary tangle formation and increased amyloid β aggregation by insulin degrading enzyme inhibition [35-38, 52, 53]. Insulin affects neuronal cognition and memory through several levels by regulating ion channels, neurotransmitter receptors and synaptic transmission in Alzheimer's disease brain [39, 40]. Amyloid β accumulation induces the oxidative stress and mitochondrial dysfunction, and these dysfunctions induces Alzheimer's disease pathogenesis [54-56]. Adiponectin is protective against amyloid β neurotoxicity in Alzheimer's disease [57]. Adiponectin modulates amyloid β in Alzheimer's disease and so improves cognition [58]. Previous studies demonstrate that the insulin sensitizing action of adiponectin may be another mechanism of neuroprotection in Alzheimer's disease [59, 60]. In conclusion, adiponectin has a important role in brain insulin dysfunction and amyloid β neurotoxicity and immune system through a variety of machanisms. Thus, adiponectin is a potential target to treat Alzheimer's disease.

Table 1. Adiponectin related diseases and pathologies

Organ/Tissue	Related disease	Related pathology	Reference
Liver/Pancreas	Diabetes	Insulin resistance/glucose metabolism dysfunction	[4, 7, 9, 15, 20-22, 25, 26, 28-36]
Heart	Cardiovascular disease	Hypertension/hyperlipidemia/atherosclerosis	[20, 21, 23]
Nervous system	Alzheimer's disease	Mild cognitive impairment/brain insulin system dysfunction/ Aβ accumulation/immune dysfunction	[6, 10, 11, 19-27, 47, 48, 50, 52-54]
Adipose tissue	Obesity	Fatty acid catabolisdysfunction/inflammation/ whole-body energy homeostasis/adiposity	[4, 9, 14, 21, 29, 31, 32, 41, 42]

http://dx.doi.org/10.5115/acb.2013.46.4.229

Future Perspective

Adiponectin associates with various disease including diabetes, obesity, cardiovascular disease and neurodegenerative diseases. Adiponectin plays multiple roles for enhancing related pathologies such as insulin resistance, hypertention, hyperlipidemia, inflammation, cognitive impairment, atherosclerosis (Table 1). Specifically, adiponectin regulates the sensitivity of insulin and modulates the immune system and enhances memory and cognitive impairment known as common pathologies of Alzheimer's disease. Thus, adiponectin may be a promising therapeutic target to alleviate Alzheimer's disease pathologies such as apoptosis and cognitive decline and dysfunctional brain insulin system.

Acknowledgements

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MEST) (2011-0017276). This work was supported by the Brain Korea 21 Project for Medical Science, Yonsei University.

References

1. Spranger J, Verma S, Göhring I, Bobbert T, Seifert J, Sindler AL, Pfeiffer A, Hileman SM, Tschöp M, Banks WA. Adiponectin does not cross the blood-brain barrier but modifies cytokine expression of brain endothelial cells. Diabetes 2006;55:141-7.
2. Kubota N, Yano W, Kubota T, Yamauchi T, Itoh S, Kumagai H, Kozono H, Takamoto I, Okamoto S, Shiuchi T, Suzuki R, Satoh H, Tsuchida A, Moroi M, Sugi K, Noda T, Ebinuma H, Ueta Y, Kondo T, Araki E, Ezaki O, Nagai R, Tobe K, Terauchi Y, Ueki K, Minokoshi Y, Kadowaki T. Adiponectin stimulates AMP-activated protein kinase in the hypothalamus and increases food intake. Cell Metab 2007;6:55-68.
3. Psilopanagioti A, Papadaki H, Kranioti EF, Alexandrides TK, Varakis JN. Expression of adiponectin and adiponectin receptors in human pituitary gland and brain. Neuroendocrinology 2009;89:38-47.
4. Calvani M, Scarfone A, Granato L, Mora EV, Nanni G, Castagneto M, Greco AV, Manco M, Mingrone G. Restoration of adiponectin pulsatility in severely obese subjects after weight loss. Diabetes 2004;53:939-47.
5. Diniz BS, Teixeira AL, Campos AC, Miranda AS, Rocha NP, Talib LL, Gattaz WF, Forlenza OV. Reduced serum levels of adiponectin in elderly patients with major depression. J Psychiatr Res 2012;46:1081-5.
6. Zuliani G, Ranzini M, Guerra G, Rossi L, Munari MR, Zurlo A, Volpato S, Atti AR, Blè A, Fellin R. Plasma cytokines profile in older subjects with late onset Alzheimer's disease or vascular dementia. J Psychiatr Res 2007;41:686-93.
7. Berg AH, Combs TP, Scherer PE. ACRP30/adiponectin: an adipokine regulating glucose and lipid metabolism. Trends Endocrinol Metab 2002;13:84-9.
8. Kadowaki T, Yamauchi T. Adiponectin and adiponectin receptors. Endocr Rev 2005;26:439-51.
9. Tsao TS, Lodish HF, Fruebis J. ACRP30, a new hormone controlling fat and glucose metabolism. Eur J Pharmacol 2002;440:213-21.
10. Cai H, Cong WN, Ji S, Rothman S, Maudsley S, Martin B. Metabolic dysfunction in Alzheimer's disease and related neurodegenerative disorders. Curr Alzheimer Res 2012;9:5-17.
11. Chen B, Liao WQ, Xu N, Xu H, Wen JY, Yu CA, Liu XY, Li CL, Zhao SM, Campbell W. Adiponectin protects against cerebral ischemia-reperfusion injury through anti-inflammatory action. Brain Res 2009;1273:129-37.
12. Jung TW, Lee JY, Shim WS, Kang ES, Kim JS, Ahn CW, Lee HC, Cha BS. Adiponectin protects human neuroblastoma SH-SY5Y cells against acetaldehyde-induced cytotoxicity. Biochem Pharmacol 2006;72:616-23.
13. Jeon BT, Shin HJ, Kim JB, Kim YK, Lee DH, Kim KH, Kim HJ, Kang SS, Cho GJ, Choi WS, Roh GS. Adiponectin protects hippocampal neurons against kainic acid-induced excitotoxicity. Brain Res Rev 2009;61:81-8.
14. Qi Y, Takahashi N, Hileman SM, Patel HR, Berg AH, Pajvani UB, Scherer PE, Ahima RS. Adiponectin acts in the brain to decrease body weight. Nat Med 2004;10:524-9.
15. Reaven GM. Insulin resistance and human disease: a short history. J Basic Clin Physiol Pharmacol 1998;9:387-406.
16. Kusminski CM, McTernan PG, Schraw T, Kos K, O'Hare JP, Ahima R, Kumar S, Scherer PE. Adiponectin complexes in human cerebrospinal fluid: distinct complex distribution from serum. Diabetologia 2007;50:634-42.
17. Kos K, Harte AL, da Silva NF, Tonchev A, Chaldakov G, James S, Snead DR, Hoggart B, O'Hare JP, McTernan PG, Kumar S. Adiponectin and resistin in human cerebrospinal fluid and expression of adiponectin receptors in the human hypothalamus. J Clin Endocrinol Metab 2007;92:1129-36.
18. Ebinuma H, Miida T, Yamauchi T, Hada Y, Hara K, Kubota N, Kadowaki T. Improved ELISA for selective measurement of adiponectin multimers and identification of adiponectin in human cerebrospinal fluid. Clin Chem 2007;53:1541-4.
19. Une K, Takei YA, Tomita N, Asamura T, Ohrui T, Furukawa K, Arai H. Adiponectin in plasma and cerebrospinal fluid in MCI and Alzheimer's disease. Eur J Neurol 2011;18:1006-9.
20. Dzielińska Z, Januszewicz A, Wiecek A, Demkow M, Makowiecka-Cieśla M, Prejbisz A, Kadziela J, Mielniczuk R, Florczak E, Janas J, Januszewicz M, Ruzyłło W. Decreased plasma concentration of a novel anti-inflammatory protein--adiponectin--in hypertensive men with coronary artery disease. Thromb Res 2003;110:365-9.
21. Ouchi N, Kihara S, Funahashi T, Matsuzawa Y, Walsh K. Obesity, adiponectin and vascular inflammatory disease. Curr Opin

Lipidol 2003;14:561-6.
22. Gulcelik NE, Halil M, Ariogul S, Usman A. Adipocytokines and aging: adiponectin and leptin. Minerva Endocrinol 2013;38:203-10.
23. Yokota T, Oritani K, Takahashi I, Ishikawa J, Matsuyama A, Ouchi N, Kihara S, Funahashi T, Tenner AJ, Tomiyama Y, Matsuzawa Y. Adiponectin, a new member of the family of soluble defense collagens, negatively regulates the growth of myelomonocytic progenitors and the functions of macrophages. Blood 2000;96:1723-32.
24. Wolf AM, Wolf D, Rumpold H, Enrich B, Tilg H. Adiponectin induces the anti-inflammatory cytokines IL-10 and IL-1RA in human leukocytes. Biochem Biophys Res Commun 2004;323:630-5.
25. Steen E, Terry BM, Rivera EJ, Cannon JL, Neely TR, Tavares R, Xu XJ, Wands JR, de la Monte SM. Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease: is this type 3 diabetes? J Alzheimers Dis 2005;7:63-80.
26. Rivera EJ, Goldin A, Fulmer N, Tavares R, Wands JR, de la Monte SM. Insulin and insulin-like growth factor expression and function deteriorate with progression of Alzheimer's disease: link to brain reductions in acetylcholine. J Alzheimers Dis 2005;8:247-68.
27. Vingtdeux V, Davies P, Dickson DW, Marambaud P. AMPK is abnormally activated in tangle- and pre-tangle-bearing neurons in Alzheimer's disease and other tauopathies. Acta Neuropathol 2011;121:337-49.
28. Ceddia RB, Somwar R, Maida A, Fang X, Bikopoulos G, Sweeney G. Globular adiponectin increases GLUT4 translocation and glucose uptake but reduces glycogen synthesis in rat skeletal muscle cells. Diabetologia 2005;48:132-9.
29. Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, Mori Y, Ide T, Murakami K, Tsuboyama-Kasaoka N, Ezaki O, Akanuma Y, Gavrilova O, Vinson C, Reitman ML, Kagechika H, Shudo K, Yoda M, Nakano Y, Tobe K, Nagai R, Kimura S, Tomita M, Froguel P, Kadowaki T. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Med 2001;7:941-6.
30. Kubota N, Terauchi Y, Yamauchi T, Kubota T, Moroi M, Matsui J, Eto K, Yamashita T, Kamon J, Satoh H, Yano W, Froguel P, Nagai R, Kimura S, Kadowaki T, Noda T. Disruption of adiponectin causes insulin resistance and neointimal formation. J Biol Chem 2002;277:25863-6.
31. Hu E, Liang P, Spiegelman BM. AdipoQ is a novel adipose-specific gene dysregulated in obesity. J Biol Chem 1996;271:10697-703.
32. Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, Tataranni PA. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab 2001;86:1930-5.
33. Statnick MA, Beavers LS, Conner LJ, Corominola H, Johnson D, Hammond CD, Rafaeloff-Phail R, Seng T, Suter TM, Sluka JP, Ravussin E, Gadski RA, Caro JF. Decreased expression of apM1 in omental and subcutaneous adipose tissue of humans with type 2 diabetes. Int J Exp Diabetes Res 2000;1:81-8.
34. Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, Iwahashi H, Kuriyama H, Ouchi N, Maeda K, Nishida M, Kihara S, Sakai N, Nakajima T, Hasegawa K, Muraguchi M, Ohmoto Y, Nakamura T, Yamashita S, Hanafusa T, Matsuzawa Y. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. Arterioscler Thromb Vasc Biol 2000;20:1595-9.
35. Craft S, Asthana S, Newcomer JW, Wilkinson CW, Matos IT, Baker LD, Cherrier M, Lofgreen C, Latendresse S, Petrova A, Plymate S, Raskind M, Grimwood K, Veith RC. Enhancement of memory in Alzheimer disease with insulin and somatostatin, but not glucose. Arch Gen Psychiatry 1999;56:1135-40.
36. Park CR, Seeley RJ, Craft S, Woods SC. Intracerebroventricular insulin enhances memory in a passive-avoidance task. Physiol Behav 2000;68:509-14.
37. van der Heide LP, Ramakers GM, Smidt MP. Insulin signaling in the central nervous system: learning to survive. Prog Neurobiol 2006;79:205-21.
38. Plum L, Schubert M, Brüning JC. The role of insulin receptor signaling in the brain. Trends Endocrinol Metab 2005;16:59-65.
39. Wang YT, Salter MW. Regulation of NMDA receptors by tyrosine kinases and phosphatases. Nature 1994;369:233-5.
40. van der Heide LP, Kamal A, Artola A, Gispen WH, Ramakers GM. Insulin modulates hippocampal activity-dependent synaptic plasticity in a N-methyl-d-aspartate receptor and phosphatidyl-inositol-3-kinase-dependent manner. J Neurochem 2005;94:1158-66.
41. Hotamisligil GS, Peraldi P, Budavari A, Ellis R, White MF, Spiegelman BM. IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF-alpha- and obesity-induced insulin resistance. Science 1996;271:665-8.
42. Winer S, Chan Y, Paltser G, Truong D, Tsui H, Bahrami J, Dorfman R, Wang Y, Zielenski J, Mastronardi F, Maezawa Y, Drucker DJ, Engleman E, Winer D, Dosch HM. Normalization of obesity-associated insulin resistance through immunotherapy. Nat Med 2009;15:921-9.
43. Nishimura S, Manabe I, Nagasaki M, Eto K, Yamashita H, Ohsugi M, Otsu M, Hara K, Ueki K, Sugiura S, Yoshimura K, Kadowaki T, Nagai R. CD8+ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. Nat Med 2009;15:914-20.
44. Semple RK, Halberg NH, Burling K, Soos MA, Schraw T, Luan J, Cochran EK, Dunger DB, Wareham NJ, Scherer PE, Gorden P, O'Rahilly S. Paradoxical elevation of high-molecular weight adiponectin in acquired extreme insulin resistance due to insulin receptor antibodies. Diabetes 2007;56:1712-7.
45. Ahima RS, Qi Y, Singhal NS, Jackson MB, Scherer PE. Brain adipocytokine action and metabolic regulation. Diabetes 2006;55 Suppl 2:S145-54.
46. Hivert MF, Sullivan LM, Fox CS, Nathan DM, D'Agostino RB Sr, Wilson PW, Meigs JB. Associations of adiponectin, resistin, and tumor necrosis factor-alpha with insulin resistance. J Clin

http://dx.doi.org/10.5115/acb.2013.46.4.229

Endocrinol Metab 2008;93:3165-72.
47. Forlenza OV, Diniz BS, Talib LL, Mendonça VA, Ojopi EB, Gattaz WF, Teixeira AL. Increased serum IL-1beta level in Alzheimer's disease and mild cognitive impairment. Dement Geriatr Cogn Disord 2009;28:507-12.
48. Diniz BS, Teixeira AL, Ojopi EB, Talib LL, Mendonça VA, Gattaz WF, Forlenza OV. Higher serum sTNFR1 level predicts conversion from mild cognitive impairment to Alzheimer's disease. J Alzheimers Dis 2010;22:1305-11.
49. Poehlman ET, Dvorak RV. Energy expenditure in Alzheimer's disease. J Nutr Health Aging 1998;2:115-8.
50. Giordano V, Peluso G, Iannuccelli M, Benatti P, Nicolai R, Calvani M. Systemic and brain metabolic dysfunction as a new paradigm for approaching Alzheimer's dementia. Neurochem Res 2007;32:555-67.
51. Yan Z, Feng J. Alzheimer's disease: interactions between cholinergic functions and beta-amyloid. Curr Alzheimer Res 2004;1:241-8.
52. Craft S, Asthana S, Schellenberg G, Cherrier M, Baker LD, Newcomer J, Plymate S, Latendresse S, Petrova A, Raskind M, Peskind E, Lofgreen C, Grimwood K. Insulin metabolism in Alzheimer's disease differs according to apolipoprotein E genotype and gender. Neuroendocrinology 1999;70:146-52.
53. Kern W, Peters A, Fruehwald-Schultes B, Deininger E, Born J, Fehm HL. Improving influence of insulin on cognitive functions in humans. Neuroendocrinology 2001;74:270-80.
54. Moreira PI, Duarte AI, Santos MS, Rego AC, Oliveira CR. An integrative view of the role of oxidative stress, mitochondria and insulin in Alzheimer's disease. J Alzheimers Dis 2009;16:741-61.
55. Bonda DJ, Wang X, Perry G, Nunomura A, Tabaton M, Zhu X, Smith MA. Oxidative stress in Alzheimer disease: a possibility for prevention. Neuropharmacology 2010;59:290-4.
56. Praticò D, Uryu K, Leight S, Trojanoswki JQ, Lee VM. Increased lipid peroxidation precedes amyloid plaque formation in an animal model of Alzheimer amyloidosis. J Neurosci 2001;21:4183-7.
57. Chan KH, Lam KS, Cheng OY, Kwan JS, Ho PW, Cheng KK, Chung SK, Ho JW, Guo VY, Xu A. Adiponectin is protective against oxidative stress induced cytotoxicity in amyloid-beta neurotoxicity. PLoS One 2012;7:e52354.
58. Reger MA, Watson GS, Green PS, Wilkinson CW, Baker LD, Cholerton B, Fishel MA, Plymate SR, Breitner JC, DeGroodt W, Mehta P, Craft S. Intranasal insulin improves cognition and modulates beta-amyloid in early AD. Neurology 2008;70:440-8.
59. Oh DK, Ciaraldi T, Henry RR. Adiponectin in health and disease. Diabetes Obes Metab 2007;9:282-9.
60. Deepa SS, Dong LQ. APPL1: role in adiponectin signaling and beyond. Am J Physiol Endocrinol Metab 2009;296:E22-36.