Biometals (2018) 31:705–714
https://doi.org/10.1007/s10534-018-0134-2

Iron metabolism in diabetes-induced Alzheimer's disease: a focus on insulin resistance in the brain

Ji Yeon Chung · Hyung-Seok Kim · Juhyun Song

Received: 11 May 2018 / Accepted: 18 June 2018 / Published online: 24 July 2018

Abstract Alzheimer's disease (AD) is characterized by an excessive accumulation of toxic amyloid beta (Aβ) plaques and memory dysfunction. The onset of AD is influenced by age, genetic background, and impaired glucose metabolism in the brain. Several studies have demonstrated that diabetes involving insulin resistance and glucose tolerance could lead to AD, ultimately resulting in cognitive dysfunction. Even though the relationship between diabetes and AD was indicated by significant evidences, the critical mechanisms and metabolic alterations in diabetes induced AD are not clear until now. Recently, iron metabolism has been shown to play multiple roles in the central nervous system (CNS). Iron deficiency and overload are associated with neurodegenerative diseases. Iron binds to Aβ and subsequently regulates Aβ toxicity in the CNS. In addition, previous studies have shown that iron is involved in the aggravation of insulin resistance. Considering these effects of iron metabolism in CNS, we expect that iron metabolism may play crucial roles in diabetic AD brain. Thus, we review the recent evidence regarding the relationship between diabetes-induced AD and iron metabolism.

Keywords Iron · Diabetes · Alzheimer's disease (AD) · Amyloid beta (Aβ) · Insulin resistance

Introduction

Iron contributes to the transportation of oxygen and regulation of cell growth, electron transport and DNA synthesis (Finch 1994; Jehn et al. 2004). Impaired iron homeostasis could result in the excessive production of reactive oxygen species (ROS) and apoptosis (Apostolakis and Kypraiou 2017). In addition, the accumulation of iron contributes to protein misfolding and aggregation, which can lead to multiple diseases (Uversky et al. 2001). Iron gradually accumulates in the brain with age, a process normally associated with changes in iron metabolism (Zecca et al. 2004). The reduction of iron overload using iron chelation therapy has been shown to alter glycemic control in individuals with type 2 diabetes (T2DM) (Swaminathan et al. 2007). One cross-sectional study reported a negative correlation between serum ferritin levels (known as the critical regulator in iron transport and strorage) (Leitner and Connor 2012) and insulin sensitivity

J. Y. Chung
Department of Neurology, Chosun University School of Medicine and Hospital, Gwangju 61452, South Korea

H.-S. Kim (✉)
Department of Forensic Medicine, Chonnam National University Medical School, Gwangju 61469, South Korea
e-mail: veritas@jnu.ac.kr

J. Song (✉)
Department of Anatomy, Chonnam National University Medical School, Gwangju 61469, South Korea
e-mail: juhyunsong@chonnam.ac.kr

(Fernandez-Real et al. 2007). In the central nervous system (CNS), transferrin accounts for approximately 0.4% of the total protein in the brain (Leitner and Connor 2012) and is observed predominantly in white matter (Gebril et al. 2011). Previous in vivo studies have shown that oral administration of iron during brain development triggers memory deficits and induces brain damage in rats (de Lima et al. 2005; Schroder et al. 2001). Current studies have reported that brain iron deposits aggravate cognitive decline in a neurodegenerative disease model (Daugherty and Raz 2015) and higher levels of brain iron deposit in gray matter triggers cognitive dysfunction (Rodrigue et al. 2013). In individuals with mild cognitive impairment (MCI) and Alzheimer's disease (AD), increased iron levels have been observed in the cortex (Smith et al. 2010). Other research has demonstrated that improvement in iron metabolism may prevent amyloid beta (Aβ) aggregation and ultimately enhance cognition (Adlard et al. 2008). Iron can bind to Aβ (Bousejra-ElGarah et al. 2011) and tau protein (Lei et al. 2017) in the brain. The binding of iron with Aβ induces the aggregation of Aβ and tau hyperphosphorylation (Yamamoto et al. 2002). Consequently, iron could affect the onset and progression of AD in humans. However, the mechanisms of iron accumulation in AD remain unclear. In this paper, we review significant evidence on the influence of iron metabolism on cognitive decline in diabetes-induced AD, and suggest that, similar to the results of an in vivo study that examined the effects of a high fat diet, a common factor between AD and T2DM is the presence of insulin resistance in the brain (Moroz et al. 2008). Taken together, there is a strong relationship between iron metabolism and diabetes-induced AD in terms of the improvement in insulin resistance and the clearance of Aβ in the AD brain. Here, we review recent evidence on the role of iron metabolism in diabetes-induced AD.

Alzheimer's disease, impaired glucose metabolism, and insulin resistance

Alzheimer's disease is the most common neurodegenerative disease and is characterized by cognitive decline, gross atrophy of the cortex and hippocampus, and the aggregation of Aβ and hyperphosphorylated tau (Ramirez-Bermudez 2012; Schubert et al. 2004). It is thought to be various factors affecting the onset and progression of AD, including age, sex, and genetic background (Ramirez-Bermudez 2012; Reitz et al. 2011). Recent research has reported a link between metabolic homeostasis and cognitive decline in obese individuals (Shefer et al. 2013). A large amount of insulin is transported into the brain via movement of cerebrospinal fluid (CSF) across the blood brain barrier (BBB) through saturable and temperature-sensitive mechanisms (Burns et al. 2007; Erol 2008). Insulin acts through its receptors, which are common in the cerebral cortex, hippocampus, cerebellum, and hypothalamus (Hopkins and Williams 1997). Insulin has a crucial role in the brain that relates to neuromodulation, proliferation, and inhibition of neuronal loss (Russo et al. 2005). Case–control studies have demonstrated that insulin resistance (IR) caused by obesity is involved in impaired cognitive function, including both memory function and attention (Maayan et al. 2011), and is associated with an increased risk of dementia (Kodl and Seaquist 2008; Whitmer et al. 2008). In the CNS, insulin influences synaptogenesis and synaptic plasticity and controls glucose metabolism and the secretion of the neurotransmitters involved in cognitive function (Cholerton et al. 2013). Sporadic AD has been reported to involve a state of insulin resistance (Salkovic-Petrisic and Hoyer 2007). IR accelerates neuronal loss by forming advanced glycation end-products (AGE) and ROS (Unoki and Yamagishi 2008). Streptozotocin (STZ)-injected AD models desensitize neuronal IRs and impair brain glucose metabolism, thereby impairing long-term cognitive function in AD patients (Salkovic-Petrisic and Lackovic 2003). Furthermore, AD is characterized by abnormal insulin signaling that results in an insulin-resistant state, increasing Aβ accumulation, tau hyperphosphorylation, and cognitive dysfunction (Talbot et al. 2012). Several studies have demonstrated that insulin deficiency has permissive influence over long-term potentiation (LTP) and memory function (Zhao et al. 2010), increases amyloidosis, and promotes neurobehavioral deficits (Dou et al. 2005; Wang et al. 2010). In addition, patients with T2DM have been shown to have cognitive dysfunction and increased cortical atrophy (Chen et al. 2011; McCrimmon et al. 2012). Impaired glycemic control, cognitive deficits, and a higher risk of AD have been observed in T2DM patients (Hassing et al. 2004; Ronnemaa et al. 2008; Whitmer et al. 2009). A reduced cerebral metabolic

rate of glucose has been reported in the AD brain (Small et al. 2000), which is thought to contribute to neurofibrillary tangle formation (Gong et al. 2006).

Iron in the AD brain

Increase of iron levels has been observed in neurodegenerative diseases (Gozzelino and Arosio 2016; Stankiewicz and Brass 2009) such as AD (Gozzelino and Arosio 2016; Hofer and Perry 2016). In CNS, blood brain barrier (BBB) has been known that it is formed by cerebrovascular endothelial cells (Burdo et al. 2001). One study demonstrated that iron transport into BBB is related with transferrin receptor mediated endocytosis into brain endothelial cells (Jefferies et al. 1984). Additionally, several studies have reported that transferrin receptor mediated signaling is critical the iron uptake across BBB (Beard et al. 2005; Bradbury 1997; Ke and Qian 2007; Moos et al. 2007). Recent studies reported the positive relationship between accumulation of iron in the brain region such as putamen and shrinkage of brain (Daugherty and Raz 2016). Previous studies demonstrated iron accumulation in special brain region such as basal ganglia has been observed based on MRI evidence (Kruer et al. 2012; Levi and Finazzi 2014). One MRI study has demonstrated that elevated iron level in brain are related with impaired cognitive function in obese humans (Blasco et al. 2014). Some CNS diseases, such as AD (Zecca et al. 2004) and Parkinson's disease (PD) (Oakley et al. 2007), show a relationship between neuronal loss and disturbance of iron metabolism. In AD brains, the increased accumulation of iron is commonly observed in the cortex and hippocampus, white matter areas affected by disease (Antharam et al. 2012; Raven et al. 2013). Another study demonstrated that excess free iron could generate oxidative stress in brain and also contributes the impaired iron homeostasis in AD brain (Altamura and Muckenthaler 2009). There are two forms of iron: redox-active forms such as ferrous (Fe^{2+} iron), and redox-inactive forms such as ferric (Fe^{3+} iron) (Rival et al. 2009). Ferritin, the body's major intracellular iron storage protein, is elevated in the AD brain (Quintana et al. 2006) and has been observed near AD plaques (Bishop et al. 2002; Connor et al. 1992). The aggregation state of $A\beta_{1-42}$ occurs during the binding of Fe^{2+} and Fe^{3+} and results in the generation of free radicals by activating the iron redox cycle through the Fenton reaction (Khan et al. 2006; Rival et al. 2009). Current study showed that ferritin is found in the $A\beta_{1-42}$ plaque with other proteins and lipids in AD brain (Summers et al. 2017). Several in vitro studies have shown that the coexistence of iron and Aβ reduces neuronal cell viability (Liu et al. 2011; Wan et al. 2011). Redox-active iron forms such as Fe_3O_4 have been observed in the human AD brain (Collingwood et al. 2008) and in APP/PS1 transgenic AD mice (Gallagher et al. 2012). Several studies have concluded that the loss of hippocampal integrity in the brains of AD patients is related to increased levels of ferritin (Raven et al. 2013) and decreased ferroportin levels (Raha et al. 2013). Recent study reported that high ferritin level in cerebrospinal fluid (CSF) accelerates the accumulation of Aβ levels in AD brain (Ayton et al. 2015; Quintana et al. 2006). Iron level is positively related to the neuroinflammation on neurons and microglia in AD brain (Cai and Xiao 2016; Urrutia et al. 2013). Moreover, the FerroPortiN1 (FPN1) as the main cellular iron exporter (Abboud and Haile 2000) regulates the iron deficiency or iron overload and its overexpression has been observed in AD brains (Bandyopadhyay and Rogers 2014; Myhre et al. 2013). Also, there are the important diseases in the relationship between AD and iron overload. Iron overload known as hemochromatosis influences various organs such as the liver, heart, and endocrine glands (Gulati et al. 2014; Pelusi et al. 2016). One study demonstrated that the glucose tolerance and diabetes are closely related with the stage of iron overload (Hatunic et al. 2010). Moreover, based on recent studies, the hemochromatosis is one of risk factors in the AD development (Connor et al. 2001; Lehmann et al. 2012; Mariani et al. 2013; Percy et al. 2014). Also, based on the relationship between iron metabolism and lipoprotein metabolism, APOE2, APOE3, and APOE4 could activate APP transcription and trigger the increase of amyloid beta (Aβ) synthesis (Huang et al. 2017). One study demonstrated that the usage of iron chelating drug could enhance the AD pathogenesis by regulating APP processing (Amit et al. 2017). Especially, APOE4 considered the most important genetic risk factor for AD promotes cerebral Aβ deposition (Hare et al. 2013; Kanekiyo et al. 2014; Verghese et al. 2013). Moreover, iron could be more susceptible to bind with Aβ and APOE under amyloid beta toxicity condition (Peters et al. 2015).

Furthermore, one case study demonstrated cognitive decline in association with haemochromatosis (Demarquay et al. 2000). Furthermore, imbalance of mitochondrial dynamics are associated with synaptic dysfunction in neuron and cell death in neurodegenerative diseases (Cho et al. 2010). Several studies have indicated that calcium (Ca^{2+}) signals affects mitochondrial functions by controlling the activation of Ca^{2+}-mediated proteins (Pennanen et al. 2014). Considering recent evidences, iron overload leads to the increase of intracellular Ca^{2+} and affect mitochondrial function in cultured cardiomyocytes and observed in the patients with iron overload cardiomyopathy (Horackova et al. 2000; Khamseekaew et al. 2016). Collectively, the iron overload in AD brain is the critical issue in many insights and could be broadly handled to find appropriated AD therapeutic solution. Taken together, we suggest that iron's role in the AD brain may be important in elucidating the exact mechanisms of AD pathogenesis.

Iron and insulin resistance

Iron is known to be a crucial regulator of glucose and lipid metabolism (Fernandez-Real and Manco 2014). Several studies demonstrated the strong relationship between ferritin as the standard marker for iron stores and the increase of diabetes risk (Forouhi et al. 2007; Fumeron et al. 2006; Jiang et al. 2004) such as insulin resistance (Cho et al. 2017; Krisai et al. 2016). Iron blocks the inhibition of insulin of glucose production by the liver and also insulin causes the increased ferritin synthesis in cultured glioma cells (Yokomori et al. 1991). The serum level of ferritin has been known to positively correlate with serum glucose (Fernandez-Real et al. 1998). According to clinical studies, iron overload in body has been reported that it is directly related to the development of glucose intolerance, leading to diabetes (Barbieri et al. 2001; Lao et al. 2001). Fleming et al. shown that the important genes of iron metabolism such as transporters DMT1, ferroportin, and MTP1 were changed in diabetes patients compared to normal subjects (Fleming and Sly 2002). Iron deposition in muscle reduces the uptake of glucose (Fernandez-Real and Manco 2014), and iron influences insulin-producing β-cells by increasing the expression of the iron transporter (DMT1) in the pancreas (Koch et al. 2003). One study has suggested that a possible mechanism for the relationship between serum ferritin levels and insulin resistance is linked to chronic inflammation (Shoelson et al. 2006). Therefore, a high level of serum ferritin is associated with an increase in free radicals and has an influence on insulin resistance (Esser et al. 2014; Gonzalez et al. 2006). Insulin resistance triggers the dysregulation of neuronal insulin signaling and ultimately leads to cognitive dysfunction (De Felice and Benedict 2015; Nuzzo et al. 2015). Insulin has been known to facilitate iron overload by redistribution of transferrin receptors to the cell surface (Noetzli et al. 2012). The oxidative stress by increased iron deposition in beta pancreatic and liver cells leads to insulin resistance, higher insulin secretion and glucose dysregulation (Dongiovanni et al. 2008; Fernandez-Real et al. 2002; Noetzli et al. 2012). In the liver, excessive iron interferes with glucose metabolism, by decreasing insulin extraction and impairing insulin signaling (Ferrannini 2000). Ruivard et al. reported that high fat diet could change iron metabolism (Ruivard 2009; Ruivard et al. 2009) and Meli et al. demonstrated that high fat diet fed animals promotes activity of iron regulatory protein 1 in the liver and an increase of TfR1 expression (Meli et al. 2013). Iron overload inhibits hepatic insulin extraction and the synthesis and secretion of insulin in the pancreas (Fernandez-Real and Manco 2014; Robertson and Harmon 2006). Recent studies have also reported that elevation of serum ferritin levels is linked to insulin resistance (IR) (Batchuluun et al. 2014; Chen et al. 2017). Pharm et al. demonstrated that the level of serum ferritin was positively associated with homeostatic model assessment for insulin resistance (HOMA-IR), an index of IR, in men (Pham et al. 2013). The insulin resistance leads to the high permeability of BBB and triggers cognitive decline in diabetic insulin resistance induced mouse model (Blasco et al. 2014; Takechi et al. 2017) and in AD model (Bell and Zlokovic 2009; Zlokovic 2011). In addition, brain iron overload leads to insulin resistance and subsequently cognitive decline in obesity animal and human models (Cholerton et al. 2013; Fernandez-Real and Manco 2014; Lin et al. 2013; Morris et al. 2011; Schroder et al. 2013; Shefer et al. 2013). One study demonstrated that iron deprivation may promote insulin receptor and Glut4 transcription in muscle (Summers et al. 2017). Considering previous trials, we need the further study to understand the accurate cellular mechanisms between

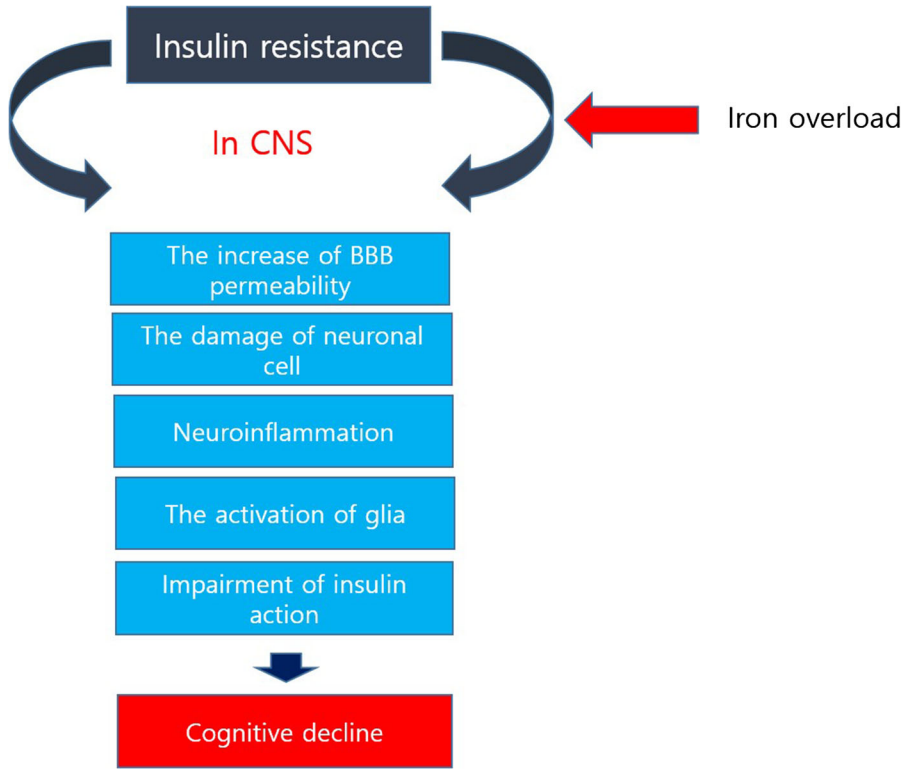

Fig. 1 The schematic image between insulin resistance caused by iron overload and AD

insulin resistance and iron metabolism in AD brain. Collectively, iron overload and deficiency are the critical issues in insulin's action and its association with insulin resistance. Given that insulin resistance could trigger cognitive impairment (Kong et al. 2018; Lamport et al. 2009; Xu et al. 2009), we speculate that the modulation of iron accumulation could improve cognitive function in AD.

Conclusions

Recently, the relationship between diabetes-induced AD has been highlighted because of the common risk factors, such as IR, between AD and T2DM. Here, we reviewed the relationship between iron metabolism and IR in the AD brain (Fig. 1). According to previous studies, iron deficiency could aggravate cognitive dysfunction by way of attention and memory dysfunction and behavioral abnormalities in obese individuals (Jauregui-Lobera 2014; Liang et al. 2014), as well as slower cognitive performance (Lubach and Coe 2008) and perturbation of cognitive development (Bourre 2006). The administration of deferoxamine used in iron overdose recovered motor and sensory nerve conduction velocity and enhanced nerve blood flow in experimental studies (Cameron and Cotter 2001). As well, chronic iron deficiency can trigger cerebral hypoxia and cognitive decline by affecting oxygen transport and storage (Demetri 2001; Petranovic et al. 2008). Although the specific mechanisms regarding the relationship between iron metabolism and cognitive function remain unclear, previous research suggests that iron metabolism is linked to memory function, neuronal survival, and IR in the CNS. Hence, we suggest that the manipulation of iron metabolism in the CNS may be a promising therapeutic approach for treating diabetes-induced AD.

Acknowledgements This study was supported by the Brain Research Program through the National Research Foundation of Korea, funded by Grant 2016R1D1A1B03930394 (Juhyun Song) and NRF-2016R1A2B4008316 (Hyung-Seok Kim).

Author contributions Ji Yeon Chung contributed to the writing of the preliminary draft of this manuscript. Hyung-Seok Kim and Juhyun Song wrote and revised the manuscript.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

References

Abboud S, Haile DJ (2000) A novel mammalian iron-regulated protein involved in intracellular iron metabolism. J Biol Chem 275:19906–19912. https://doi.org/10.1074/jbc.M000713200

Adlard PA et al (2008) Rapid restoration of cognition in Alzheimer's transgenic mice with 8-hydroxy quinoline analogs is associated with decreased interstitial Abeta. Neuron 59:43–55. https://doi.org/10.1016/j.neuron.2008.06.018

Altamura S, Muckenthaler MU (2009) Iron toxicity in diseases of aging: Alzheimer's disease, Parkinson's disease and atherosclerosis. J Alzheimer's Dis 16:879–895. https://doi.org/10.3233/JAD-2009-1010

Amit T, Bar-Am O, Mechlovich D, Kupershmidt L, Youdim MBH, Weinreb O (2017) The novel multitarget iron chelating and propargylamine drug M30 affects APP regulation and processing activities in Alzheimer's disease models. Neuropharmacology 123:359–367. https://doi.org/10.1016/j.neuropharm.2017.05.026

Antharam V et al (2012) High field magnetic resonance microscopy of the human hippocampus in Alzheimer's disease: quantitative imaging and correlation with iron. NeuroImage 59:1249–1260. https://doi.org/10.1016/j.neuroimage.2011.08.019

Apostolakis S, Kypraiou AM (2017) Iron in neurodegenerative disorders: being in the wrong place at the wrong time? Rev Neurosci. https://doi.org/10.1515/revneuro-2017-0020

Ayton S, Faux NG, Bush AI, Alzheimer's Disease Neuroimaging I (2015) Ferritin levels in the cerebrospinal fluid predict Alzheimer's disease outcomes and are regulated by APOE. Nat Commun 6:6760. https://doi.org/10.1038/ncomms7760

Bandyopadhyay S, Rogers JT (2014) Alzheimer's disease therapeutics targeted to the control of amyloid precursor protein translation: maintenance of brain iron homeostasis. Biochem Pharmacol 88:486–494. https://doi.org/10.1016/j.bcp.2014.01.032

Barbieri M, Ragno E, Benvenuti E, Zito GA, Corsi A, Ferrucci L, Paolisso G (2001) New aspects of the insulin resistance syndrome: impact on haematological parameters. Diabetologia 44:1232–1237. https://doi.org/10.1007/s001250100634

Batchuluun B, Matsumata T, Batchuluun B, Erdenebileg N, Tsagaantsooj G, Boldbaatar K, Khasag A (2014) Serum ferritin level is higher in poorly controlled patients with type 2 diabetes and people without diabetes, aged over 55 years. Diabet Med 31:419–424. https://doi.org/10.1111/dme.12343

Beard JL, Wiesinger JA, Li N, Connor JR (2005) Brain iron uptake in hypotransferrinemic mice: influence of systemic iron status. J Neurosci Res 79:254–261. https://doi.org/10.1002/jnr.20324

Bell RD, Zlokovic BV (2009) Neurovascular mechanisms and blood-brain barrier disorder in Alzheimer's disease. Acta Neuropathol 118:103–113. https://doi.org/10.1007/s00401-009-0522-3

Bishop GM, Robinson SR, Liu Q, Perry G, Atwood CS, Smith MA (2002) Iron: a pathological mediator of Alzheimer disease? Dev Neurosci 24:184–187. https://doi.org/10.1159/000065696

Blasco G et al (2014) Brain iron overload, insulin resistance, and cognitive performance in obese subjects: a preliminary MRI case-control study. Diabetes Care 37:3076–3083. https://doi.org/10.2337/dc14-0664

Bourre JM (2006) Effects of nutrients (in food) on the structure and function of the nervous system: update on dietary requirements for brain. Part 1: micronutrients. J Nutr Health Aging 10:377–385

Bousejra-ElGarah F, Bijani C, Coppel Y, Faller P, Hureau C (2011) Iron(II) binding to amyloid-beta, the Alzheimer's peptide. Inorg Chem 50:9024–9030. https://doi.org/10.1021/ic201233b

Bradbury MW (1997) Transport of iron in the blood-brain-cerebrospinal fluid system. J Neurochem 69:443–454

Burdo JR et al (2001) Distribution of divalent metal transporter 1 and metal transport protein 1 in the normal and Belgrade rat. J Neurosci Res 66:1198–1207. https://doi.org/10.1002/jnr.1256

Burns JM et al (2007) Peripheral insulin and brain structure in early Alzheimer disease. Neurology 69:1094–1104. https://doi.org/10.1212/01.wnl.0000276952.91704.af

Cai Z, Xiao M (2016) Oligodendrocytes and Alzheimer's disease. Int J Neurosci 126:97–104. https://doi.org/10.3109/00207454.2015.1025778

Cameron NE, Cotter MA (2001) Effects of an extracellular metal chelator on neurovascular function in diabetic rats. Diabetologia 44:621–628. https://doi.org/10.1007/s001250051669

Chen L, Magliano DJ, Zimmet PZ (2011) The worldwide epidemiology of type 2 diabetes mellitus–present and future perspectives. Nat Rev Endocrinol 8:228–236. https://doi.org/10.1038/nrendo.2011.183

Chen L, Li Y, Zhang F, Zhang S, Zhou X, Ji L (2017) Association of serum ferritin levels with metabolic syndrome and insulin resistance in a Chinese population. J Diabetes Complicat 31:364–368. https://doi.org/10.1016/j.jdiacomp.2016.06.018

Cho DH, Nakamura T, Lipton SA (2010) Mitochondrial dynamics in cell death and neurodegeneration. Cell Mol Life Sci 67:3435–3447. https://doi.org/10.1007/s00018-010-0435-2

Cho MR, Park JK, Choi WJ, Cho AR, Lee YJ (2017) Serum ferritin level is positively associated with insulin resistance and metabolic syndrome in postmenopausal women: a nationwide population-based study. Maturitas 103:3–7. https://doi.org/10.1016/j.maturitas.2017.06.004

Cholerton B, Baker LD, Craft S (2013) Insulin, cognition, and dementia. Eur J Pharmacol 719:170–179. https://doi.org/10.1016/j.ejphar.2013.08.008

Collingwood JF et al (2008) Three-dimensional tomographic imaging and characterization of iron compounds within Alzheimer's plaque core material. J Alzheimer's Dis 14:235–245

Connor JR, Menzies SL, St Martin SM, Mufson EJ (1992) A histochemical study of iron, transferrin, and ferritin in Alzheimer's diseased brains. J Neurosci Res 31:75–83. https://doi.org/10.1002/jnr.490310111

Connor JR et al (2001) Is hemochromatosis a risk factor for Alzheimer's disease? J Alzheimer's Dis 3:471–477

Daugherty AM, Raz N (2015) Appraising the role of iron in brain aging and cognition: promises and limitations of mri methods. Neuropsychol Rev 25:272–287. https://doi.org/10.1007/s11065-015-9292-y

Daugherty AM, Raz N (2016) Accumulation of iron in the putamen predicts its shrinkage in healthy older adults: a multi-occasion longitudinal study. NeuroImage 128:11–20. https://doi.org/10.1016/j.neuroimage.2015.12.045

De Felice FG, Benedict C (2015) A key role of insulin receptors in memory. Diabetes 64:3653–3655. https://doi.org/10.2337/dbi15-0011

de Lima MN et al (2005) Recognition memory impairment and brain oxidative stress induced by postnatal iron administration. Eur J Neurosci 21:2521–2528. https://doi.org/10.1111/j.1460-9568.2005.04083.x

Demarquay G, Setiey A, Morel Y, Trepo C, Chazot G, Broussolle E (2000) Clinical report of three patients with hereditary hemochromatosis and movement disorders. Mov Disord 15:1204–1209

Demetri GD (2001) Anaemia and its functional consequences in cancer patients: current challenges in management and prospects for improving therapy. Br J Cancer 84(Suppl 1):31–37. https://doi.org/10.1054/bjoc.2001.1750

Dongiovanni P, Valenti L, Ludovica Fracanzani A, Gatti S, Cairo G, Fargion S (2008) Iron depletion by deferoxamine up-regulates glucose uptake and insulin signaling in hepatoma cells and in rat liver. Am J Pathol 172:738–747. https://doi.org/10.2353/ajpath.2008.070097

Dou JT, Chen M, Dufour F, Alkon DL, Zhao WQ (2005) Insulin receptor signaling in long-term memory consolidation following spatial learning. Learn Mem 12:646–655. https://doi.org/10.1101/lm.88005

Erol A (2008) An integrated and unifying hypothesis for the metabolic basis of sporadic Alzheimer's disease. J Alzheimer's Dis 13:241–253

Esser N, Legrand-Poels S, Piette J, Paquot N, Scheen AJ (2014) NLRP3 inflammasome and visceral adipose tissue. Rev Med Liege 69:57–61

Fernandez-Real JM, Manco M (2014) Effects of iron overload on chronic metabolic diseases. Lancet Diabetes Endocrinol 2:513–526. https://doi.org/10.1016/S2213-8587(13)70174-8

Fernandez-Real JM et al (1998) Serum ferritin as a component of the insulin resistance syndrome. Diabetes Care 21:62–68

Fernandez-Real JM, Penarroja G, Castro A, Garcia-Bragado F, Lopez-Bermejo A, Ricart W (2002) Blood letting in high-ferritin type 2 diabetes: effects on vascular reactivity. Diabetes Care 25:2249–2255

Fernandez-Real JM, Moreno JM, Lopez-Bermejo A, Chico B, Vendrell J, Ricart W (2007) Circulating soluble transferrin receptor according to glucose tolerance status and insulin sensitivity. Diabetes Care 30:604–608. https://doi.org/10.2337/dc06-1138

Ferrannini E (2000) Insulin resistance, iron, and the liver. Lancet 355:2181–2182. https://doi.org/10.1016/S0140-6736(00)02397-7

Finch C (1994) Regulators of iron balance in humans. Blood 84:1697–1702

Fleming RE, Sly WS (2002) Mechanisms of iron accumulation in hereditary hemochromatosis. Annu Rev Physiol 64:663–680. https://doi.org/10.1146/annurev.physiol.64.081501.155838

Forouhi NG et al (2007) Elevated serum ferritin levels predict new-onset type 2 diabetes: results from the EPIC-Norfolk prospective study. Diabetologia 50:949–956. https://doi.org/10.1007/s00125-007-0604-5

Fumeron F et al (2006) Ferritin and transferrin are both predictive of the onset of hyperglycemia in men and women over 3 years: the data from an epidemiological study on the Insulin Resistance Syndrome (DESIR) study. Diabetes Care 29:2090–2094. https://doi.org/10.2337/dc06-0093

Gallagher JJ, Finnegan ME, Grehan B, Dobson J, Collingwood JF, Lynch MA (2012) Modest amyloid deposition is associated with iron dysregulation, microglial activation, and oxidative stress. J Alzheimer's Dis 28:147–161. https://doi.org/10.3233/JAD-2011-110614

Gebril OH, Simpson JE, Kirby J, Brayne C, Ince PG (2011) Brain iron dysregulation and the risk of ageing white matter lesions. NeuroMol Med 13:289–299. https://doi.org/10.1007/s12017-011-8161-y

Gong CX, Liu F, Grundke-Iqbal I, Iqbal K (2006) Impaired brain glucose metabolism leads to Alzheimer neurofibrillary degeneration through a decrease in tau O-GlcNAcylation. J Alzheimer's Dis 9:1–12

Gonzalez AS, Guerrero DB, Soto MB, Diaz SP, Martinez-Olmos M, Vidal O (2006) Metabolic syndrome, insulin resistance and the inflammation markers C-reactive protein and ferritin. Eur J Clin Nutr 60:802–809. https://doi.org/10.1038/sj.ejcn.1602384

Gozzelino R, Arosio P (2016) Iron homeostasis in health and disease. Int J Mol Sci 17:130. https://doi.org/10.3390/ijms17010130

Gulati V, Harikrishnan P, Palaniswamy C, Aronow WS, Jain D, Frishman WH (2014) Cardiac involvement in hemochromatosis. Cardiol Rev 22:56–68. https://doi.org/10.1097/CRD.0b013e3182a67805

Hare D, Ayton S, Bush A, Lei P (2013) A delicate balance: iron metabolism and diseases of the brain. Front Aging Neurosci 5:34. https://doi.org/10.3389/fnagi.2013.00034

Hassing LB, Hofer SM, Nilsson SE, Berg S, Pedersen NL, McClearn G, Johansson B (2004) Comorbid type 2 diabetes mellitus and hypertension exacerbates cognitive decline: evidence from a longitudinal study. Age Ageing 33:355–361. https://doi.org/10.1093/ageing/afh100

Hatunic M, Finucane FM, Brennan AM, Norris S, Pacini G, Nolan JJ (2010) Effect of iron overload on glucose metabolism in patients with hereditary hemochromatosis.

Metab Clin Exp 59:380–384. https://doi.org/10.1016/j.metabol.2009.08.006

Hofer T, Perry G (2016) Nucleic acid oxidative damage in Alzheimer's disease-explained by the hepcidin-ferroportin neuronal iron overload hypothesis? J Trace Elem Med Biol 38:1–9. https://doi.org/10.1016/j.jtemb.2016.06.005

Hopkins DF, Williams G (1997) Insulin receptors are widely distributed in human brain and bind human and porcine insulin with equal affinity. Diabet Med 14:1044–1050. https://doi.org/10.1002/(SICI)1096-9136(199712)

Horackova M, Ponka P, Byczko Z (2000) The antioxidant effects of a novel iron chelator salicylaldehyde isonicotinoyl hydrazone in the prevention of H(2)O(2) injury in adult cardiomyocytes. Cardiovasc Res 47:529–536

Huang YA, Zhou B, Wernig M, Sudhof TC (2017) ApoE2, ApoE3, and ApoE4 differentially stimulate APP transcription and abeta secretion. Cell 168(3):427–441. https://doi.org/10.1016/j.cell.2016.12.044

Jauregui-Lobera I (2014) Iron deficiency and cognitive functions. Neuropsychiatr Dis Treat 10:2087–2095. https://doi.org/10.2147/NDT.S72491

Jefferies WA, Brandon MR, Hunt SV, Williams AF, Gatter KC, Mason DY (1984) Transferrin receptor on endothelium of brain capillaries. Nature 312:162–163

Jehn M, Clark JM, Guallar E (2004) Serum ferritin and risk of the metabolic syndrome in U.S. adults. Diabetes Care 27:2422–2428

Jiang R, Manson JE, Meigs JB, Ma J, Rifai N, Hu FB (2004) Body iron stores in relation to risk of type 2 diabetes in apparently healthy women. JAMA 291:711–717. https://doi.org/10.1001/jama.291.6.711

Kanekiyo T, Xu H, Bu G (2014) ApoE and Abeta in Alzheimer's disease: accidental encounters or partners? Neuron 81:740–754. https://doi.org/10.1016/j.neuron.2014.01.045

Ke Y, Qian ZM (2007) Brain iron metabolism: neurobiology and neurochemistry. Prog Neurobiol 83:149–173. https://doi.org/10.1016/j.pneurobio.2007.07.009

Khamseekaew J, Kumfu S, Chattipakorn SC, Chattipakorn N (2016) Effects of iron overload on cardiac calcium regulation: translational insights into mechanisms and management of a global epidemic. Can J Cardiol 32:1009–1016. https://doi.org/10.1016/j.cjca.2015.10.012

Khan A, Dobson JP, Exley C (2006) Redox cycling of iron by Abeta42. Free Radic Biol Med 40:557–569. https://doi.org/10.1016/j.freeradbiomed.2005.09.013

Koch RO et al (2003) Distribution of DMT 1 within the human glandular system. Histol Histopathol 18:1095–1101. https://doi.org/10.14670/HH-18.1095

Kodl CT, Seaquist ER (2008) Cognitive dysfunction and diabetes mellitus. Endocr Rev 29:494–511. https://doi.org/10.1210/er.2007-0034

Kong SH, Park YJ, Lee JY, Cho NH, Moon MK (2018) Insulin resistance is associated with cognitive decline among older koreans with normal baseline cognitive function: a prospective community-based cohort study. Sci Rep 8:650. https://doi.org/10.1038/s41598-017-18998-0

Krisai P et al (2016) Relationships of iron metabolism with insulin resistance and glucose levels in young and healthy adults. Eur J Intern Med 32:31–37. https://doi.org/10.1016/j.ejim.2016.03.017

Kruer MC et al (2012) Neuroimaging features of neurodegeneration with brain iron accumulation. Am J Neuroradiol 33:407–414. https://doi.org/10.3174/ajnr.A2677

Lamport DJ, Lawton CL, Mansfield MW, Dye L (2009) Impairments in glucose tolerance can have a negative impact on cognitive function: a systematic research review. Neurosci Biobehav Rev 33:394–413. https://doi.org/10.1016/j.neubiorev.2008.10.008

Lao TT, Chan PL, Tam KF (2001) Gestational diabetes mellitus in the last trimester—a feature of maternal iron excess? Diabet Med 18:218–223

Lehmann DJ et al (2012) Transferrin and HFE genes interact in Alzheimer's disease risk: the Epistasis project. Neurobiol Aging 33(202):e201–213. https://doi.org/10.1016/j.neurobiolaging.2010.07.018

Lei P et al (2017) Lithium suppression of tau induces brain iron accumulation and neurodegeneration. Mol Psychiatry 22:396–406. https://doi.org/10.1038/mp.2016.96

Leitner DF, Connor JR (2012) Functional roles of transferrin in the brain. Biochem Biophys Acta 1820:393–402. https://doi.org/10.1016/j.bbagen.2011.10.016

Levi S, Finazzi D (2014) Neurodegeneration with brain iron accumulation: update on pathogenic mechanisms. Front Pharmacol 5:99. https://doi.org/10.3389/fphar.2014.00099

Liang J, Matheson BE, Kaye WH, Boutelle KN (2014) Neurocognitive correlates of obesity and obesity-related behaviors in children and adolescents. Int J Obes 38:494–506. https://doi.org/10.1038/ijo.2013.142

Lin D et al (2013) Decreased serum hepcidin concentration correlates with brain iron deposition in patients with HBV-related cirrhosis. PLoS ONE 8:e65551. https://doi.org/10.1371/journal.pone.0065551

Liu B et al (2011) Iron promotes the toxicity of amyloid beta peptide by impeding its ordered aggregation. J Biol Chem 286:4248–4256. https://doi.org/10.1074/jbc.M110.158980

Lubach GR, Coe CL (2008) Selective impairment of cognitive performance in the young monkey following recovery from iron deficiency. J Dev Behav Pediatr 29:11–17. https://doi.org/10.1097/DBP.0b013e31815f24a9

Maayan L, Hoogendoorn C, Sweat V, Convit A (2011) Disinhibited eating in obese adolescents is associated with orbitofrontal volume reductions and executive dysfunction. Obesity 19:1382–1387. https://doi.org/10.1038/oby.2011.15

Mariani S et al (2013) Effects of hemochromatosis and transferrin gene mutations on peripheral iron dyshomeostasis in mild cognitive impairment and Alzheimer's and Parkinson's diseases. Front Aging Neurosci 5:37. https://doi.org/10.3389/fnagi.2013.00037

McCrimmon RJ, Ryan CM, Frier BM (2012) Diabetes and cognitive dysfunction. Lancet 379:2291–2299. https://doi.org/10.1016/S0140-6736(12)60360-2

Meli R et al (2013) High fat diet induces liver steatosis and early dysregulation of iron metabolism in rats. PLoS ONE 8:e66570. https://doi.org/10.1371/journal.pone.0066570

Moos T, Rosengren Nielsen T, Skjorringe T, Morgan EH (2007) Iron trafficking inside the brain. J Neurochem 103:1730–1740. https://doi.org/10.1111/j.1471-4159.2007.04976.x

Moroz N, Tong M, Longato L, Xu H, de la Monte SM (2008) Limited Alzheimer-type neurodegeneration in

experimental obesity and type 2 diabetes mellitus. J Alzheimer's Dis 15:29–44
Morris JK et al (2011) Insulin resistance impairs nigrostriatal dopamine function. Exp Neurol 231:171–180. https://doi.org/10.1016/j.expneurol.2011.06.005
Myhre O, Utkilen H, Duale N, Brunborg G, Hofer T (2013) Metal dyshomeostasis and inflammation in Alzheimer's and Parkinson's diseases: possible impact of environmental exposures. Oxid Med Cell Longev 2013:726954. https://doi.org/10.1155/2013/726954
Noetzli LJ, Mittelman SD, Watanabe RM, Coates TD, Wood JC (2012) Pancreatic iron and glucose dysregulation in thalassemia major. Am J Hematol 87:155–160. https://doi.org/10.1002/ajh.22223
Nuzzo D et al (2015) Insulin resistance as common molecular denominator linking obesity to Alzheimer's disease. Curr Alzheimer Res 12:723–735
Oakley AE et al (2007) Individual dopaminergic neurons show raised iron levels in Parkinson disease. Neurology 68:1820–1825. https://doi.org/10.1212/01.wnl.0000262033.01945.9a
Pelusi C, Gasparini DI, Bianchi N, Pasquali R (2016) Endocrine dysfunction in hereditary hemochromatosis. J Endocrinol Invest 39:837–847. https://doi.org/10.1007/s40618-016-0451-7
Pennanen C et al (2014) Mitochondrial fission is required for cardiomyocyte hypertrophy mediated by a Ca2 + -calcineurin signaling pathway. J Cell Sci 127:2659–2671. https://doi.org/10.1242/jcs.139394
Percy M et al (2014) Risk factors for development of dementia in a unique six-year cohort study. I. An exploratory, pilot study of involvement of the E4 allele of apolipoprotein E, mutations of the hemochromatosis-HFE gene, type 2 diabetes, and stroke. J Alzheimer's Dis 38:907–922. https://doi.org/10.3233/JAD-131409
Peters DG, Connor JR, Meadowcroft MD (2015) The relationship between iron dyshomeostasis and amyloidogenesis in Alzheimer's disease: two sides of the same coin. Neurobiol Dis 81:49–65. https://doi.org/10.1016/j.nbd.2015.08.007
Petranovic D, Batinac T, Petranovic D, Ruzic A, Ruzic T (2008) Iron deficiency anaemia influences cognitive functions. Med Hypotheses 70:70–72. https://doi.org/10.1016/j.mehy.2007.04.029
Pham NM et al (2013) Serum ferritin is associated with markers of insulin resistance in Japanese men but not in women. Metab Clin Exp 62:561–567. https://doi.org/10.1016/j.metabol.2012.07.025
Quintana C et al (2006) Study of the localization of iron, ferritin, and hemosiderin in Alzheimer's disease hippocampus by analytical microscopy at the subcellular level. J Struct Biol 153:42–54. https://doi.org/10.1016/j.jsb.2005.11.001
Raha AA, Vaishnav RA, Friedland RP, Bomford A, Raha-Chowdhury R (2013) The systemic iron-regulatory proteins hepcidin and ferroportin are reduced in the brain in Alzheimer's disease. Acta Neuropathol Commun 1:55. https://doi.org/10.1186/2051-5960-1-55
Ramirez-Bermudez J (2012) Alzheimer's disease: critical notes on the history of a medical concept. Arch Med Res 43:595–599. https://doi.org/10.1016/j.arcmed.2012.11.008
Raven EP, Lu PH, Tishler TA, Heydari P, Bartzokis G (2013) Increased iron levels and decreased tissue integrity in hippocampus of Alzheimer's disease detected in vivo with magnetic resonance imaging. J Alzheimer's Dis 37:127–136. https://doi.org/10.3233/JAD-130209
Reitz C, Brayne C, Mayeux R (2011) Epidemiology of Alzheimer disease. Nat Rev Neurol 7:137–152. https://doi.org/10.1038/nrneurol.2011.2
Rival T et al (2009) Fenton chemistry and oxidative stress mediate the toxicity of the beta-amyloid peptide in a Drosophila model of Alzheimer's disease. Eur J Neurosci 29:1335–1347. https://doi.org/10.1111/j.1460-9568.2009.06701.x
Robertson RP, Harmon JS (2006) Diabetes, glucose toxicity, and oxidative stress: a case of double jeopardy for the pancreatic islet beta cell. Free Radic Biol Med 41:177–184. https://doi.org/10.1016/j.freeradbiomed.2005.04.030
Rodrigue KM, Daugherty AM, Haacke EM, Raz N (2013) The role of hippocampal iron concentration and hippocampal volume in age-related differences in memory. Cereb Cortex 23:1533–1541. https://doi.org/10.1093/cercor/bhs139
Ronnemaa E et al (2008) Impaired insulin secretion increases the risk of Alzheimer disease. Neurology 71:1065–1071. https://doi.org/10.1212/01.wnl.0000310646.32212.3a
Ruivard M (2009) Genetic iron overloads and hepatic insulin-resistance iron overload syndrome: an update. La Rev Med Interne 30:35–42. https://doi.org/10.1016/j.revmed.2008.05.004
Ruivard M et al (2009) Iron absorption in dysmetabolic iron overload syndrome is decreased and correlates with increased plasma hepcidin. J Hepatol 50:1219–1225. https://doi.org/10.1016/j.jhep.2009.01.029
Russo VC, Gluckman PD, Feldman EL, Werther GA (2005) The insulin-like growth factor system and its pleiotropic functions in brain. Endocr Rev 26:916–943. https://doi.org/10.1210/er.2004-0024
Salkovic-Petrisic M, Hoyer S (2007) Central insulin resistance as a trigger for sporadic Alzheimer-like pathology: an experimental approach. In: Neuropsychiatric disorders an integrative approach. Springer, Vienna, pp 217–233
Salkovic-Petrisic M, Lackovic Z (2003) Intracerebroventricular administration of betacytotoxics alters expression of brain monoamine transporter genes. J Neural Transm 110:15–29. https://doi.org/10.1007/s00702-002-0773-9
Schroder N, Fredriksson A, Vianna MR, Roesler R, Izquierdo I, Archer T (2001) Memory deficits in adult rats following postnatal iron administration. Behav Brain Res 124:77–85
Schroder N, Figueiredo LS, de Lima MN (2013) Role of brain iron accumulation in cognitive dysfunction: evidence from animal models and human studies. J Alzheimer's Dis 34:797–812. https://doi.org/10.3233/JAD-121996
Schubert M et al (2004) Role for neuronal insulin resistance in neurodegenerative diseases. Proc Natl Acad Sci USA 101:3100–3105. https://doi.org/10.1073/pnas.0308724101
Shefer G, Marcus Y, Stern N (2013) Is obesity a brain disease? Neurosci Biobehav Rev 37:2489–2503. https://doi.org/10.1016/j.neubiorev.2013.07.015
Shoelson SE, Lee J, Goldfine AB (2006) Inflammation and insulin resistance. J Clin Investig 116:1793–1801. https://doi.org/10.1172/JCI29069
Small GW et al (2000) Cerebral metabolic and cognitive decline in persons at genetic risk for Alzheimer's disease. Proc Natl

Acad Sci USA 97:6037–6042. https://doi.org/10.1073/pnas.090106797

Smith MA et al (2010) Increased iron and free radical generation in preclinical Alzheimer disease and mild cognitive impairment. J Alzheimer's Dis 19:363–372. https://doi.org/10.3233/JAD-2010-1239

Stankiewicz JM, Brass SD (2009) Role of iron in neurotoxicity: a cause for concern in the elderly? Curr Opin Clin Nutr Metab Care 12:22–29. https://doi.org/10.1097/MCO.0b013e32831ba07c

Summers KL et al (2017) A multimodal spectroscopic imaging method to characterize the metal and macromolecular content of proteinaceous aggregates ("amyloid plaques"). Biochemistry 56:4107–4116. https://doi.org/10.1021/acs.biochem.7b00262

Swaminathan S, Fonseca VA, Alam MG, Shah SV (2007) The role of iron in diabetes and its complications. Diabetes Care 30:1926–1933. https://doi.org/10.2337/dc06-2625

Takechi R et al (2017) Blood-brain barrier dysfunction precedes cognitive decline and neurodegeneration in diabetic insulin resistant mouse model: an implication for causal link. Front Aging Neurosci 9:399. https://doi.org/10.3389/fnagi.2017.00399

Talbot K et al (2012) Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. J Clin Investig 122:1316–1338. https://doi.org/10.1172/JCI59903

Unoki H, Yamagishi S (2008) Advanced glycation end products and insulin resistance. Curr Pharm Des 14:987–989

Urrutia P et al (2013) Inflammation alters the expression of DMT1, FPN1 and hepcidin, and it causes iron accumulation in central nervous system cells. J Neurochem 126:541–549. https://doi.org/10.1111/jnc.12244

Uversky VN, Li J, Fink AL (2001) Metal-triggered structural transformations, aggregation, and fibrillation of human alpha-synuclein. A possible molecular NK between Parkinson's disease and heavy metal exposure. J Biol Chem 276:44284–44296. https://doi.org/10.1074/jbc.M105343200

Verghese PB et al (2013) ApoE influences amyloid-beta (Abeta) clearance despite minimal apoE/Abeta association in physiological conditions. Proc Natl Acad Sci USA 110:E1807–1816. https://doi.org/10.1073/pnas.1220484110

Wan L, Nie G, Zhang J, Luo Y, Zhang P, Zhang Z, Zhao B (2011) β-Amyloid peptide increases levels of iron content and oxidative stress in human cell and *Caenorhabditis elegans* models of Alzheimer disease. Free Radic Biol Med 50:122–129. https://doi.org/10.1016/j.freeradbiomed.2010.10.707

Wang X, Zheng W, Xie JW, Wang T, Wang SL, Teng WP, Wang ZY (2010) Insulin deficiency exacerbates cerebral amyloidosis and behavioral deficits in an Alzheimer transgenic mouse model. Mol Neurodegener 5:46. https://doi.org/10.1186/1750-1326-5-46

Whitmer RA, Gustafson DR, Barrett-Connor E, Haan MN, Gunderson EP, Yaffe K (2008) Central obesity and increased risk of dementia more than three decades later. Neurology 71:1057–1064. https://doi.org/10.1212/01.wnl.0000306313.89165.ef

Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP Jr, Selby JV (2009) Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. JAMA 301:1565–1572. https://doi.org/10.1001/jama.2009.460

Xu WL, von Strauss E, Qiu CX, Winblad B, Fratiglioni L (2009) Uncontrolled diabetes increases the risk of Alzheimer's disease: a population-based cohort study. Diabetologia 52:1031–1039. https://doi.org/10.1007/s00125-009-1323-x

Yamamoto A, Shin RW, Hasegawa K, Naiki H, Sato H, Yoshimasu F, Kitamoto T (2002) Iron (III) induces aggregation of hyperphosphorylated tau and its reduction to iron (II) reverses the aggregation: implications in the formation of neurofibrillary tangles of Alzheimer's disease. J Neurochem 82:1137–1147

Yokomori N, Iwasa Y, Aida K, Inoue M, Tawata M, Onaya T (1991) Transcriptional regulation of ferritin messenger ribonucleic acid levels by insulin in cultured rat glioma cells. Endocrinology 128:1474–1480. https://doi.org/10.1210/endo-128-3-1474

Zecca L, Youdim MB, Riederer P, Connor JR, Crichton RR (2004) Iron, brain ageing and neurodegenerative disorders. Nat Rev Neurosci 5:863–873. https://doi.org/10.1038/nrn1537

Zhao W, Wu X, Xie H, Ke Y, Yung WH (2010) Permissive role of insulin in the expression of long-term potentiation in the hippocampus of immature rats. Neuro-Signals 18:236–245. https://doi.org/10.1159/000324040

Zlokovic BV (2011) Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. Nat Rev Neurosci 12:723–738. https://doi.org/10.1038/nrn3114