DEMENTIAS - REVIEW ARTICLE

The link between iron, metabolic syndrome, and Alzheimer's disease

Edna Grünblatt · Jasmin Bartl · Peter Riederer

Abstract Both Alzheimer's disease (AD), the most common form of dementia, and type-2 diabetes mellitus (T2DM), a disease associated with metabolic syndrome (MetS), affect a great number of the world population and both have increased prevalence with age. Recently, many studies demonstrated that pre-diabetes, MetS, and T2DM are risk factors in the development of AD and have many common mechanisms. The main focus of studies is the insulin resistance outcome found both in MetS as well as in brains of AD subjects. However, oxidative stress (OS)-related mechanisms, which are well known to be involved in AD, including mitochondrial dysfunction, elevated iron concentration, reactive oxygen species (ROS), and stress-related enzyme or proteins (e.g. heme oxygenase-1, transferrin, etc.), have not been elucidated in MetS or T2DM brains although OS and iron are involved in the degeneration of the pancreatic islet β cells. Therefore, this review sets to cover the current literature regarding OS and iron in MetS and T2DM and the similarities to mechanisms in AD both in human subjects as well as in animal models.

E. Grünblatt (✉)
Department of Child and Adolescent Psychiatry,
University of Zurich, Neumuensterallee 9,
8032 Zurich, Switzerland
e-mail: Gruenblatt_E@klinik.uni-wuerzburg.de

E. Grünblatt · J. Bartl · P. Riederer
Neurochemistry Laboratory, Clinical Neurochemistry,
Clinic and Policlinic for Psychiatry, Psychosomatic
and Psychotherapy, National Parkinson Foundation Centre
of Excellence Laboratories, University of Würzburg,
Füchsleinstr. 15, 97080 Würzburg, Germany

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most important and prevalent chronic diseases. It currently affects 250 million people worldwide, with 6 million new cases reported each year (Cole et al. 2007). This prevalence rises with age from 12% in people aged 65–70 to 15% in people over age 80 (Wild et al. 2004). T2DM is a systemic disease that can damage any organ in the body (Campbell 2009). Resembling diabetes, cognitive dysfunction, especially Alzheimer's disease (AD), represents another serious problem and is rising in prevalence worldwide, especially among the elderly (Alzheimer's 2010). Early onset of T2DM, poor glycemic control and the presence of micro- and macrovascular disease may interact to produce early cognitive deficits (Awad et al. 2004; Ronnemaa et al. 2008, 2009). Several studies have reported a high risk of AD in patients with T2DM (Ott et al. 1996, 1999; Leibson et al. 1997; Hassing et al. 2004a; Whitmer 2007). In addition, the co-morbid hypertension and overweight were found to be linked to risk of dementia (Hassing et al. 2004b, 2009; Luchsinger and Gustafson 2009; Whitmer et al. 2008).

Many studies suggest that the risk of cognitive decline and neurodegeneration is increased not only in T2DM, but also in patients with pre-diabetes and metabolic syndrome (MetS) (Luchsinger 2008). Individuals with pre-diabetes are defined as those presenting with impaired fasting glucose and/or impaired glucose tolerance (Yaffe et al. 2004), which increases their risk of developing frank T2DM.

These subjects already present with insulin resistance as a pathophysiological mechanism that is often associated with MetS (Yaffe et al. 2004; Luchsinger 2008). MetS, in turn, is a cluster of interrelated cardiometabolic risk factors including visceral obesity, dyslipidemia (elevated triglycerides and/or low HDL-cholesterol), hypertension, dysglycemia (pre-diabetes or diabetes) (Spalding et al. 2009). MetS was initially defined by the World Health Organization (WHO) in 1998 (Alberti and Zimmet 1998). The prevalence of MetS varies depending on population. In Europe as well as in the United States the prevalence increases with age (Potenza and Mechanick 2009).

It has been suggested that an increase in the plasma concentration of insulin while fasting was associated with AD both in people with and without diabetes, which suggests that insulin resistance, independent of diabetes, may increase disease risk (Luchsinger et al. 2004; Kuusisto et al. 1997). Consistent reductions in the regional cerebral metabolic rate of glucose were also reported to exist in AD brain (Fukuyama et al. 1994; Haense et al. 2009; Herholz 2003). However, this diminished glucose utilization was not attributed to an insufficient supply of glucose to the brain, but rather to diminished glucose breakdown in brain tissue caused by a disturbance in the control of glucose utilization at the level of insulin signal transduction (Hoyer 2004). Studies of hippocampal volume revealed a link between insulin resistance and cognitive performance (Rasgon et al. 2009). Indeed, insulin-receptors density is up-regulated in AD showing an impairment of the insulin signal transduction cascade similar to that seen in T2DM (Frölich et al. 1998). These results suggest that sporadic AD is the "insulin-resistant brain state" (IRBS) (Hoyer 1998; Salkovic-Petrisic and Lackovic 2005). Insulin resistance seems also to accelerate biological aging by fostering the formation of advanced glycation end-products (AGE) and, consequently, reactive oxygen species (ROS) (Smith et al. 1995; Munch et al. 1997). The relation between insulin and the metabolism of amyloid-β peptide (Aβ) and tau protein hyperphosphorylation in particular has been receiving increasing attention over the past few years (Gasparini and Xu 2003; Craft 2007, 2009).

However, the common mechanism involving iron and oxidative stress (OS) is not yet a focus of attention. One epidemiological study suggested the common etiology in regard to induction of nitrosamine-OS in AD, T2DM as well as in non-alcoholic steatohepatitis (de la Monte et al. 2009). Recently, a shift toward linking T2DM and AD is becoming rather mainstream. But some years ago, it was still controversial in regard to the involvement of vascular components, such as AGE and OS in AD (Smith et al. 1996b). Therefore, in this review we attempt to cover the current knowledge with regard to OS and iron involvement both in AD and in T2DM.

Oxidative stress

Oxidative stress (OS) is characterized by a compromise in the physiological removal of ROS and/or an increase in their production that results from irreversible damage to biomacromolecules. Oxidative damage of biomacromolecules has been described in the brains of AD patients: (1) DNA and RNA oxidation is marked by increased levels of 8-hydroxy-2-deoxyguanosine and 8-hydroxyguanosine (Nunomura et al. 1999, 2001); (2) protein oxidation is marked by elevated levels of protein carbonyl and nitration of tyrosine residues (Smith et al. 1996a); (3) lipid peroxidation is marked by high levels of thiobarbituric acid-reactive substances (TBARS), malondialdehyde (MDA), 4-hydroxy-2-nonenal (HNE), and isoprostanes and altered phospholipid composition (Sayre et al. 1997); and (4) modification to sugars is marked by increased glycation and glycoxidation (Smith et al. 1994b). The brain of AD patients, in particular the hippocampus and amygdala, is hallmarked by increased OS as demonstrated by the elevated activities of antioxidant proteins, such as glutathione reductase, glutathione peroxidase, superoxide dismutase, and catalase (Perry et al. 2002).

In T2DM it is debated whether the involvement of mitochondrial dysfunction may cause OS and cell destruction in the pancreatic β-cells (Sivitz and Yorek 2010). It was reported recently, that redox-sensitive cellular signaling systems play an important role in the development, progressive nature (remodeling), and damaging effects on the β-cell within the islet of the pancreas (Hayden and Tyagi 2002; Perez-Matute et al. 2009).

Iron accumulation in AD and T2DM

Iron is an essential component of proteins containing iron–sulfur clusters, heme, and diiron-oxo metal centers that are involved in important cellular processes like oxygen transport, mitochondrial respiration, or DNA synthesis (Rausch et al. 1988). Severe iron deficiency will cause growth arrest and cell death. Iron is a transition metal that can serve both as an electron donor and acceptor. In living organisms, iron can be found in its reduced ferrous (Fe^{2+}) and its oxidized ferric (Fe^{3+}) states. The same chemical properties that make iron a highly versatile component in numerous biological processes can cause toxicity if iron is unshielded. Excess free iron is involved in the Fenton redox reaction which catalyzes the conversion of ROS to the highly reactive hydroxyl radical (OH·) that will damage DNA, proteins, and lipids. Because iron excess and deficiency are equally detrimental for the cell, regulatory mechanisms have evolved to maintain iron homeostasis

both at the cellular and at the systemic levels (Hentze et al. 2004).

Iron progressively accumulates in the brain with age (Zecca et al. 2004), which is normally associated to changes in iron metabolism and/or homeostasis. Iron accumulation affects protein modification, misfolding, and aggregation (Hashimoto et al. 1999a, b; Uversky et al. 2001). Besides, it has an important effect on production of radical species and eventually OS (Uversky et al. 2001; Zecca et al. 2004; Hirose et al. 2003).

In AD it was observed that iron accumulates in the same brain regions that are characterized by amyloid-β (Aβ) deposition, such as hippocampus, parietal cortex, and motor cortex (Good et al. 1992; Dedman et al. 1992; Connor et al. 1992b; LeVine 1997). In addition, iron accumulation was also observed in neurons with neurofibrillary tangles (NFT) (Smith et al. 1997). Recently, increased iron both in cortex and in cerebellum of pre-clinical AD/mild cognitive impaired (MCI) cases was found (Smith et al. 2010). Interestingly, binding of ferric iron to the tau protein precedes the aggregation of hyper-phosphorylated tau and the subsequent formation of NFT (Yamamoto et al. 2002). Aβ is a metalloprotein that binds transition metal ions through three histidine residues located in the N-terminal domain (Nakamura et al. 2007; Atwood et al. 2000). Metal binding remotes Aβ aggregation (Bush 2003; House et al. 2004; Loske et al. 2000) and in the absence of metal ions Aβ is unable to aggregate (Barrow et al. 1992; Faller 2009). A second link between iron homeostasis and AD is based on the observation that AβPP expression is iron regulated; AβPP levels increase upon iron treatment and decrease upon addition of an iron chelator in neuroblastoma cells (Rogers et al. 2002). Interestingly, disease progression of T2DM correlates with amylin deposition, which, similar to Aβ and tau, undergoes a change in tertiary structure and is finally deposited in insulin-producing pancreatic islet β-cells (Hoppener et al. 2000). Amylin is also known as islet amyloid polypeptide (IAPP). In a recent study, human amylin induced significant increase in producing ROS via inhibition of mitochondrial complex IV similarly to Aβ (Lim et al. 2010).

Accumulating evidence suggests that iron plays a pathogenic role in T2DM and its complications, such as microangiopathy and atherosclerosis (Swaminathan et al. 2007; Rajpathak et al. 2009). In addition to the induction of OS, iron may also impede insulin extraction in the liver, impair pancreatic insulin secretion, and interfere with insulin action and glucose uptake in adipocytes. Of note, a reduction in iron overload with either phlebotomy or iron chelation therapy has been shown to reverse or improve glycemic control in T2DM (Swaminathan et al. 2007). Experimental studies have indicated that iron deficiency is related to increased insulin sensitivity in animals (Borel

et al. 1993; Farrell et al. 1988), while epidemiological studies have reported an association between iron overload and peripheral insulin resistance (Dandona et al. 1983). Interestingly, elevated body iron stores were recently suggested to be a component of the MetS (Fernandez-Real et al. 1999).

Transferrin and ferritin in AD and T2DM

Transferrin (for iron mobilization) and ferritin (for iron storage) are well-known proteins involved in iron transport and storage. Transferrin accounts for approximately 0.4% of the total protein in the brain (Connor et al. 1992b) and is found predominantly in white matter or areas high in white matter (Connor et al. 1987, 1992b). At the cellular level, transferrin is localized mainly in oligodendrocytes (Connor et al. 1990) although neuronal immunostaining has also been reported (Oh et al. 1986). Ferritin levels in the human brain are 10 times higher than transferrin (Connor et al. 1992b). Connor et al. (1992a) demonstrated in AD human brains that transferrin and ferritin in general are found predominantly in oligodendrocytes. Transferrin is homogenously distributed around the senile plaques and is apparently extracellular. In addition, transferrin is found in astrocytes in the cerebral cortical white matter of the Alzheimer's tissue rather than its normal distribution in oligodendrocytes. A robust ferritin immunoreaction accompanies senile plaques and many blood vessels in the Alzheimer's brain tissue. Although many ferritin-positive oligodendrocytes are present in the Alzheimer's tissue, most of the ferritin-containing cells associated with senile plaques and blood vessels are microglia (Connor et al. 1992a).

Alterations in ferritin or transferrin are also reported for T2DM. For example, in a cross-sectional study of Finnish men, it was reported that men with the highest quintile of ferritin had 21.6% higher levels of insulin and 6.1% higher levels of glucose (Tuomainen et al. 1997). Other investigators reported that the association of ferritin with insulin sensitivity (assessed by hyperinsulinemic euglycemic clamp) was independent of body mass index (BMI) and other relevant factors (Fernandez-Real et al. 1998, 2007). Similarly, several other cross-sectional studies have also reported an inverse correlation between serum ferritin levels and measures of insulin sensitivity (Fernandez-Real et al. 2007; Haap et al. 2003). In addition to the potential effect of iron on insulin action, insulin may also affect iron metabolism. In vitro data suggest that insulin is capable of redistributing transferrin receptor to the cell surface leading to increased cellular iron uptake in adipose tissue and the liver (Davis et al. 1986; Tanner and Lienhard 1987). This effect of insulin on the up-regulation of iron uptake occurs

concurrently with its effect on glucose uptake (Tanner and Lienhard 1989). This finding has been further substantiated by experiments in rats which have shown that insulin injection leads to increased serum levels of soluble transferrin receptor (Clairmont and Czech 1990). Thus, hyperinsulinemia in states of insulin resistance may contribute to high circulating soluble transferrin receptor levels. This hypothesis is supported by a recent study among Caucasian men in which a significant inverse correlation between soluble transferrin receptor levels and insulin sensitivity was reported (Fernandez-Real et al. 2007). Moreover, increasing evidence suggests that serum ferritin, a good indicator of body iron stores, is positively associated with MetS (Jehn et al. 2004; Choi et al. 2005).

Metallothionein in AD and T2DM

Metallothionein (MT) research in the brain has shown that this family of proteins plays a major role in brain physiology (Hidalgo et al. 2001). There are four closely linked *MT* genes (MT-I-IV) present in rodents (Quaife et al. 1994; Palmiter et al. 1992). Metallothionein-I and metallothionein-II (MT-I&II) are expressed coordinately in most tissues including those of the CNS (Campagne et al. 2000), while metallothionein-III (MT-III) and metallothionein-IV (MT-IV) show a much more restricted tissue expression (primarily localized in the CNS and stratified squamous epithelia, respectively). There is compelling evidence that MT-I&II are involved in the response of the brain to damage (Hidalgo et al. 2001), and indeed there is a significant up-regulation of MT-I/MT-II proteins in a number of human neurological diseases, including AD (Chuah and Getchell 1999; Adlard et al. 1998; Zambenedetti et al. 1998; Hidalgo et al. 2006), while MT-III seems to decrease in AD subjects (Yu et al. 2001).

In T2DM, MT was found to protect islets β-cells from most kinds of ROS (Li et al. 2004a, b).

Heme oxygenase-1 in AD and T2DM

Heme oxygenases localize within the endoplasmatic reticulum where they function, in association with NADPH cytochrome P450 reductase, to oxidize heme to biliverdin, free ferrous iron, and carbon monoxide (CO). Two isoforms of heme oxygenase, HO-1 and HO-2, exist in mammals. HO-1 expresses in the brain in few neurons and neuroglia (Baranano and Snyder 2001). It was shown that HO-1 induction, as consequence of OS, may protect cells by enhancing the breakdown of pro-oxidant heme to the radical-scavenging bile pigments, biliverdin, and bilirubin (Baranano and Snyder 2001; Nakagami et al. 1993; Dore

et al. 1999). In AD brain, HO-1 protein co-localizes to astrocytes, neurons, NFT, senile plaques, corpora amylacea, ependymocytes, choroid plexus epithelial cells, and some endothelial and vascular smooth muscle cells (Smith et al. 1994a; Schipper et al. 1995). In AD hippocampus an increased immunoreactive HO-1 in astrocytes was found (Schipper et al. 1995). Even in postmortem brain samples of MCI, HO-1 was found to increase (Schipper et al. 2006).

In T2DM it was demonstrated in mononuclear cells, that the HO-1 gene expression was significantly higher in patients compared to controls (Avogaro et al. 2003). Additionally, these authors demonstrated reduction of HO-1 expression after metabolic normalization in some of the patients (Avogaro et al. 2003).

Animal model

Streptozotocin (STZ) is a naturally produced antibiotic from *Streptomyces achromogenes*, which is widely used to induce experimental diabetes in mice. Its biological effect lies in the susceptibility of pancreas islets to the drug, which enters the cytoplasm via the glucose transporter GLUT2 (Wang and Gleichmann 1998; Schnedl et al. 1994). Several deleterious effects of STZ have been reported including DNA methylation (Murata et al. 1999), protein modification (Bidasee et al. 2003), and ROS generation (Chen et al. 2001; Gille et al. 2002). It was found that treating STZ-diabetic mice with $ZnSO_4$ significantly up-regulated MT production in pancreatic islets, which in parallel prevented tissue degeneration and STZ-diabetes induction (Ohly et al. 2000). The protective role of MT is also demonstrated by the reduction of STZ-induced DNA damage, degranulation and cell death of pancreatic β-cells in transgenic mice over-expressing MT-1 upon STZ treatment (Chen et al. 2001). In a recent study, it was reported that treatment of STZ-diabetic mice with Zn reversed the increased levels of iron and MT caused by STZ in the periphery (e.g. urine, liver, pancreas, and kidney) as well as in the CNS (cerebellum and midbrain) (Beltramini et al. 2006). These authors found again a protective effect of Zn that was demonstrated both in the periphery as well as in the CNS. In STZ-induced T2DM rats, it was shown that caloric restriction could significantly reduce triglyceride, ROS, and inflammation in the brain (Ugochukwu et al. 2006). The antioxidant enzyme, glutathione peroxidase was reduced as consequence of diabetes induction, while caloric restriction reversed this effect (Ugochukwu et al. 2006).

Considering the presence of insulin and insulin-receptors in the brain, an experimental rat model was developed by using intracerebroventricular (icv) STZ to induce the IRBS (Hoyer et al. 1994). This was found to cause prolonged

impairment of brain glucose and energy metabolism, decreased choline acetyltransferase levels in the hippocampus as well as impairment in learning and memory (Lannert and Hoyer 1998; Zeevalk et al. 1998; Hoyer et al. 1999, 2000; Hoyer and Lannert 1999; Hoyer 1997). In the last decade, this model was extensively investigated at molecular, pathological, and neurochemical levels and it is notable that many features of this model resemble alterations occurring in AD (de la Monte and Wands 2008; Salkovic-Petrisic and Hoyer 2007; Grünblatt et al. 2004, 2006, 2007; Salkovic-Petrisic et al. 2006; Moreira et al. 2004; Shoham et al. 2003, Salkovic-Petrisic and Lackovic 2003, Plaschke et al. 2010; de la Monte and Tong 2009; Tong et al. 2009). Interestingly, it was found that STZ-icv causes decrease of MT-I&II gene expression in the cortex and striatum, while increase in the cerebellum which might indicate specific sensitivity of cortex and putamen to OS (Grünblatt et al. 2006). Another indication of OS in STZ-icv rats is the findings of significant elevations of malondialdehyde levels and decreased glutathione levels in various brain regions (Sharma and Gupta 2001, 2002; Ishrat et al. 2009).

In an obesity/T2DM mouse model, using high fat diet, Moroz et al. demonstrated a link between AD and T2DM showing that both present insulin resistance in the brain, but still where not fully similar to the neuropathology in AD (Moroz et al. 2008).

In another mice model for T2DM (db/db CBL57) it was found that anti-oxidative defence enzymes, such as superoxide dismutase, catalase, and glutathione-S-transferase were significantly lower in the brains than in control animals (Makar et al. 1995). In addition, the amount of polyunsaturated fatty acids was increased in brains of these animals (Makar et al. 1995). These facts point to the susceptibility of these diabetic mice to OS and ROS not only in the periphery, but also in the brain.

Another link between AD pathology and diabetes is the ferric nitrilotriacetate (Fe-NTA)-induced diabetes in rats. (Fe-NTA), an iron chelate, induces carcinoma in the kidneys after intermittent injection and causes diabetes, one of the symptoms of hemochromatosis (Li et al. 1987; Awai et al. 1979). A unique characteristic of Fe-NTA is that it generates free radicals without reducing ferric to ferrous iron (Kawabata et al. 1986), while reduction with H_2O_2 induces hydroxyl radicals in a Fenton reaction. In addition, Fe-NTA causes rapid increase in free iron and a higher content in the serum compared with other iron chelates (Liu et al. 1991). Using this model, it was found that iron was accumulating in the cortex and the hypothalamus, rather than in other areas of the brain (Nakatsuka et al. 2009). HO-1 was induced both in the cortex and in the hypothalamus, while muscarinic acetylcholine receptor mRNAs were suppressed in the cortex (Nakatsuka et al. 2009).
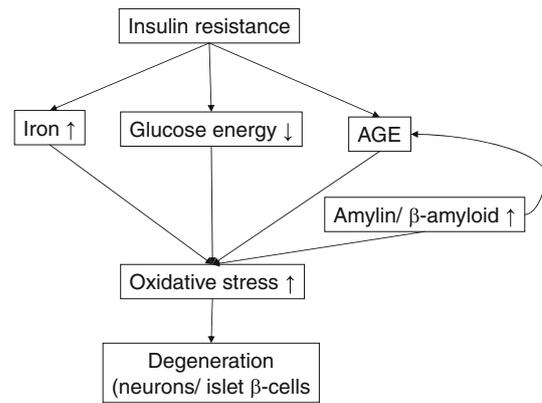

Fig. 1 Common factors involved both in Alzheimer's disease and in metabolic syndrome including type 2 Diabetes mellitus

Conclusion

From the current literature, it becomes clear that iron involvement both in AD and in T2DM is common and causes degeneration of either neurons of islet β-cells in the pancreas. It is probably not far fetched to hypothesize that MetS causing insulin resistance leads to increase in iron stores in the pancreas as well as in sensitive brain regions which then further may induce T2DM and AD (for the communalities see Fig. 1). The mechanisms of action, which then cause aggregation of amyloid plaques or amylin are strikingly similar in which both cause further toxicity in the cells. Still, the brains of T2DM were very scarcely investigated for OS markers including iron, HO-1, or MT; therefore, it would be of interest linking these alterations known to be involved in AD to T2DM. To do this, further experimental work is essential.

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