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The diabetic brain and cognition

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Abstract The prevalence of both Alzheimer's disease (AD) and vascular dementia (VaD) is increasing with the aging of the population. Studies from the last several years have shown that people with diabetes have an increased risk for dementia and cognitive impairment. Therefore, the authors of this consensus review tried to elaborate on the role of diabetes, especially diabetes type 2 (T2DM) in both AD and VaD. Based on the clinical and experimental work of scientists from 18 countries participating in the International Congress on Vascular Disorders and on literature search using PUBMED, it can be concluded that T2DM is a risk factor for both, AD and VaD, based on a pathology of glucose utilization. This pathology is the consequence of a disturbance of insulin-related mechanisms leading to brain insulin resistance. Although the underlying pathological mechanisms for AD and VaD are different in many aspects, the contribution of T2DM and insulin resistant brain state (IRBS) to cerebrovascular disturbances in both disorders

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cannot be neglected. Therefore, early diagnosis of metabolic parameters including those relevant for T2DM is required. Moreover, it is possible that therapeutic options utilized today for diabetes treatment may also have an effect on the risk for dementia. T2DM/IRBS contribute to pathological processes in AD and VaD.

Keywords Vascular dementia · Alzheimer's disease · Diabetes mellitus · Insulin resistance · Cognition · Neurotransmitters in dementia · Diabetic brain · Pathology of dementia · Experimental model of dementia · Neurogenesis in dementia · Epidemiology of dementive disorders · Imaging in dementia

Abbreviations

Aβ	Beta-amyloid-protein
AChE	Acetylcholinesterase
AD	Alzheimer's disease
AGEs	Advanced glycation end products
AKT1s1	Proline-rich AKT1 substrate 1
AKT-1	RAC-alpha serine/threonine-protein kinase
AKT-2	RAC-beta serine/threonine-protein kinase
APP	Beta-amyloid precursor protein
APOE ε4	Apolipoprotein E ε4
AQP4	Aquaporin-4
ATP	Adenosine triphospate
BBB	Blood brain barrier
BChE	Butyrylcholinesterase
BHB	Beta-hydroxybutyrate
BIR	Brain insulin resistance
CBF	Cerebral blood flow
CBH	Chronic brain hypoperfusion
CSF	Cerebrospinal fluid
Ct	Control
CVR	Cerebrovascular reactivity
DM	Diabetes mellitus
DNA	Desoxyribonucleic acid
FDG	Fluorodeoxyglucose
FTO	Fat-mass and obesity-associated gene
Gd-DTPA	Gadolinium-based MRI contrast agent
GLP-1	Glucagon-like peptide 1
GLUT3	Glucose transporter 3
GM	Grey matter
GSK3β	Glycogen synthase kinase 3 β
HOMA-IR	Homeostatic model assessment of insulin resistance
HNE	4-Hydroxynonenal
IDE	Insulin degrading enzyme
ICV	Intracerebroventricular
IGF-1R	Insulin-like growth factor 1 receptor
IR	Insulin receptor
IRBS	Insulin resistant brain state
IRβ	Insulin receptor subunit β
IRS1	Insulin receptor substrate-1
IRS-1pS616	Serin-phosphorylated insulin receptor substrate-1

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IRS2	Insulin receptor substrate-2
ISF	Interstitial fluid
KAT	Kynurenine aminotransferase
KYNAC	Kynurenic acid
MCI	Mild cognitive impairment
MRI	Magnet resonance imaging
mTOR	Mechanistic target of rapamycin
OS	Oxidative stress
PCAD	Pre-clinical AD
PET	Positron emission tomography
PG	Postprandial glycemia
PIK3CB	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta isoform
PIK3CD	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta
PI3	Phosphatidylinositol-3-kinase
PI3K	Phosphoinositid-3-kinase
PIP3	Phosphatidylinositol (3,4,5)-triphosphate
PPARγ	Peroxisome proliferator-activated receptor gamma
P-Tau	Phospho-Tau-Protein
PYY	Peptide YY
P53	Phosphoprotein p53
QA	Quinolinic acid
RAGE	Receptor for AGEs
RNA	Ribonucleic acid
ROS	Reactive oxygen species
sAD	Sporadic Alzheimer's disease
SGLT2	Sodium/glucose cotransporter 2
STZ	Streptozotocin
T2DM	Type 2 diabetes mellitus
T1DM	Type 1 diabetes mellitus
VaD	Vascular dementia
WM	White matter

Introduction

A causative association between diabetes mellitus (DM) and cognitive impairment has been suggested based on clinical, epidemiological, and experimental studies (Alafuzoff et al. 2009; Bitel et al. 2012; Vagelatos and Eslick 2013; Carvalho et al. 2015; Feinkohl et al. 2015; Jellinger 2015a).

In fact, recent studies demonstrate a pathophysiological link between diabetes mellitus type II (T2DM) and cognitive decline (Jellinger 2015b). This is demonstrated in persons with DM showing that a higher risk of developing Alzheimer's disease (AD), vascular dementia (VaD) and mixed-type dementia (AD plus cerebrovascular disease), and comorbidity, in particular cerebrovascular disease, hypertension, hypercholesterolemia, etc. increases this risk (Jellinger 2015b; Haroon et al. 2015; Kuo et al. 2015). Insulin resistance predicts medial temporal hypermetabolism in Mild Cognitive Impairment (MCI) conversion to AD (Willette et al. 2015b). In addition, changes in glucose uptake in medial temporal regions in AD predict worse memory performance (Willette et al. 2015a). Moreover, DM facilitates cognitive decline in patients with mild AD compared to those without comorbid DM (Jellinger 2015a; Ascher-Svanum et al. 2015). However, the precise mechanisms involved in the development of AD in diabetics are not yet fully understood, and several pathogenic pathways have been discussed (Feinkohl et al. 2015; Abner et al. 2016; Hao et al. 2015; Chiu et al. 2015; Verdile et al. 2015; Bedse et al. 2015; De Felice et al. 2014), including vascular brain disease, insulin resistance, and other metabolic effects on the brain.

In a meta-analysis, Chatterjee et al. (2016) estimated the sex-specific relationship between women and men with DM with incident dementia. Fourteen studies with 2310.330 individuals and 102.174 dementia cases were

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included. T2DM showed a ~60% greater risk for the development of dementia compared with those without DM. For VaD but not for non-vascular dementia, the additional risk is greater in women (Chatterjee et al. 2016).

In the study of Marseglia et al. (2016), the authors aimed to identify the cognitive domains initially impaired by diabetes and the factors that play a role in this first stage. There were 2.305 cognitively intact participants aged ≥60 years. A variety of memory tests were assessed. Diabetes (controlled and uncontrolled) as well as prediabetes were ascertained by clinicians. Information on vascular disorders and vascular risk factors has been recorded. Mainly uncontrolled diabetes in APOEε4 non-carriers was related to lower performance in perceptual speed, category fluency, and digit scan forward, and this association was present only among participants with vascular disorders or vascular risk factors (Marseglia et al. 2016).

One-fifth of dementia cases are caused by VaD, a disorder with heterogenous spectrum of cerebrovascular pathologies (Nizam and Hyer 2007). VaD is one of the most prevalent dementia disorders after AD (Ozbabalik et al. 2012). The prevalence of VaD rises rapidly between ages 65–85. People with DM as compared to those without DM have a higher risk for developing VaD [pooled RR 2.27 [95% CI 1.94–2.66] (Gudala et al. 2013) and 2.2 (95% CI 1.7–2.8)] (Ninomiya 2014). They are 2–4 times more likely to develop AD and have a 1.5–2-fold greater risk for an accelerated rate of age-related cognitive decline (Cukierman et al. 2005). This has been demonstrated utilizing both neuropsychological instruments and surrogates such as change in MRI volumes (van den Berg et al. 2010; van Harten et al. 2006; Reijmer et al. 2011). Individuals with elevated blood glucose levels are at an increased risk to develop dementia, and those with elevated blood glucose levels have a more pronounced conversion from MCI to AD, suggesting that disrupted glucose homeostasis could play a more causal role in AD pathogenesis (Macauley et al. 2015).

Observational studies have also shown an increase in the incidence of other types of dementia than AD or VaD in DM (Gudala et al. 2013; Macauley et al. 2015; Irie et al. 2008; Ahtiluoto et al. 2010). Therefore, the precise mechanisms involved in the development of cognitive impairment in diabetic patients are not yet fully understood (Alafuzoff et al. 2009; Feinkohl et al. 2015).

Advances in the management of T2DM have enhanced preventive and medical services and have diminished its macro- and microvascular complications. This has led to an increase in life expectancy of people with diabetes, however, that has increased the population at risk for cognitive impairment and dementia (Ninomiya 2014).

Given all these aspects, the group concluded that disrupted glucose homeostasis is of risk for developing dementia. This includes diabetes-dependent cerebrovascular pathology. Therefore, the cascade of pathological events in AD may show first onset of non-vascular pathology followed by cerebrovascular changes, while for VaD, cerebrovascular pathology is of primary importance.

Possible mechanisms for the relationship between diabetes and cognitive impairment

Is cognitive impairment in patients with diabetes mellitus type 1 (T1DM) a consequence of vascular impairment or a separate process?

Modest cognitive impairment in patients with T1DM does not follow any dementia pattern. Compared to healthy controls, patients with T1DM were slower in information-processing, but had better scores on visuospatial tests (Brands et al. 2006). It was shown that patients with T1DM have an increased risk of lacunar stroke (Luitse et al. 2012) and those with additional microangiopathy had decreased structural connectivity in posterior brain regions (van Duinkerken et al. 2012a) and impaired function in the ventral attention network (Van Duinkerken et al. 2012b). However, the effect of vascular lesions on the cognitive decline in T1DM patients is not entirely clear (Brands et al. 2006; Nunley et al. 2015; Biessels and Reijmer 2014; Huang et al. 2014). In contrast to T2DM, T1DM begins earlier in life and may influence brain development (Biessels et al. 2008; de Felice and Benedict 2015) via insulin receptors in the hypothalamus, which play a key role in the memory system (De Felice et al. 2014; de Felice and Benedict 2015). In a recent small study, patients with T1DM had partly altered CSF AD biomarkers (Ouwens et al. 2014). Levels of p-Tau were elevated similar to those in AD patients. Another biomarker is soluble low-density lipoprotein receptor-related protein 1 (sLRP1) protein, which regulates efflux of beta-amyloid (Aβ) from the brain to the blood and is impaired in patients with AD (Ramanathan et al. 2015). T1DM patients who had elevated levels of sLRP1 in the CSF, performed better on the cognitive tests (Ouwens et al. 2014).

Hyperglycemia, which is a primary impairment in T1DM, can cause permanent cognitive impairment, thus contrasting the situation with hypoglycemia. In the brain of streptozotocin (STZ)–T1DM rats and mice decreased neurogenesis (Alvarez et al. 2009), mitochondrial dysfunction due to decreased activity of respiratory chain complex I (Taurino et al. 2012), lower release of adenosine triphosphate (ATP) and downregulation of synaptic purinergic receptors in the hippocampus (Duarte et al. 2007), a region involved in learning and memory (Duarte et al. 2007), have been reported. Moreover, STZ–T1DM animals performed poorly on cognitive tasks (Alvarez et al. 2009).

Taken together, it is likely that vascular risk factors together with metabolic causes may facilitate neurodegeneration and contribute to cognitive impairment in T1DM patients.

Atherosclerosis, stroke, and insulin resistance

Several pathogenic routes have been suggested for this relationship. First, chronic hyperglycemia may cause cognitive impairments and abnormalities in synaptic plasticity (Jacobson et al. 2007). Tight glycemic control significantly reduced the rate of brain atrophy over a period of 40 months in STZ-induced diabetic rats compared with the standard glucose treatment (Biessels et al. 1996). Second, relative insulin deficiency (also termed "insulin resistance") may be of importance. The Hisayama study reported an increase in the presence of neuritic plaques with higher postprandial glycemic (PG) levels, fasting insulin level, and insulin resistance in AD (Doi et al. 2010), which might be also relevant for mixed forms of dementia with VaD involvement. It is reasonable to postulate a close association between 2-h PG levels and the risk of VaD, because increased 2-h PG levels are associated with the development of stroke (Thacker et al. 2011; Doi et al. 2010). Insulin resistance is associated with VaD through atherosclerosis (De Felice et al. 2014; Fitzpatrick et al. 2009). Obesity in T2DM contributes to hyperinsulinemia and insulin resistance. Insulin also regulates acetylcholine synthesis (Kimura et al. 2016), thus possibly affecting cognitive functions in dementia. Insulin resistance reduces the amount of insulin that crosses the blood–brain barrier (BBB), which hinders its role in the brain (see details in glycemic control). It has been found that prolonged hyperinsulinemia induces an impaired response to insulin through decreased expression of insulin receptors at the BBB and brain and consequently inhibits the insulin transport into cerebrospinal fluid (CSF) and brain tissues (Neumann et al. 2008). These changes could cause deficits in learning and memory formation, probably due to a neuroglial energy crisis (Kimura 2001, 2016; Craft et al. 1998). Higher levels of plasma insulin provoke amyloid accumulation by limiting the degradation of Aβ by direct competition for the insulin degrading enzyme (IDE), which degrades both insulin and Aβ (Neumann et al. 2008). However, lower insulin levels in CSF and the impaired response to insulin and insulin-like growth factor-1 inhibit the transportation of these carrier proteins and decrease the clearance of Aβ (Craft and Watson 2004). Third, chronic exposure to hyperglycemia in DM also induces abnormalities in the cerebral capillaries (termed "vasculopenia") (Serlin et al. 2011). Recent human study in asymptomatic, late middle-aged adults ($N = 186$) from the Registry for Alzheimer's Prevention who underwent [C-11]Pittsburgh compound B (PiB) position emission tomography as an indicator of amyloid deposition in the brain tested the interaction between insulin resistance and glycemic status on PiB distribution volume in the cerebral cortex (Willette et al. 2015a). The results of that study demonstrated that in normoglycemia, higher peripheral insulin resistance corresponded to higher PiB uptake in frontal and temporal areas, indicating that in individuals at risk for AD, peripheral insulin resistance may contribute to and predicts brain amyloid deposition in brain regions affected by AD. Since this association was not confirmed in a much smaller study on 47 participants (Thambisetty et al. 2013), further studies are needed to resolve the nature of the link between insulin resistance/T2DM and amyloid load. On the other hand, peripheral insulin resistance has been found to predict MCI progression to AD, as shown by the study of the Alzheimer's Disease Neuroimaging Initiative which included 194 MCI, 60 AD, and 26 cognitively normal subjects (Willette et al. 2015b). The results suggested that during the MCI stage, the homeostatic model assessment of insulin resistance (HOMA-IR) as an index of peripheral insulin resistance is differently associated with either hypo- or hyper- glucose (FDG-PET) metabolism in different brain areas, depending on whether participants progress to develop clinical AD. Therefore, evidence accumulated showing that peripheral insulin resistance, which is often associated with a metabolic syndrome and T2DM, has a role in prediction of AD pathology development, but its most specific AD correlates have not been clearly defined yet.

Finally, severe hypoglycemia may be also a risk factor for cognitive impairments in patients with DM. It has been reported that patients with recurrent severe hypoglycemic episodes have a 1.5–2.0 times greater risk of the development or deterioration of cognitive impairment (Thacker et al. 2011). These are, however, prospective studies, and as cognitive impairment is a long process, it is hard to delineate the direction of the relationship, i.e., does cognitive impairment cause severe hypoglycemia or does severe hypoglycemia cause dementia. Older patients are thought to have less brain reserve or brain plasticity than younger patients (Artola et al. 2002). Therefore, it is plausible that hypoglycemia could cause neurologic changes that render an older patient more susceptible to dementia.

Glycemic control

Peripheral insulin of pancreatic origin crosses the BBB in a tightly controlled manner, as the BBB expresses insulin receptors, which may decrease in number in response to specific conditions associated with chronic hyperinsulinemia and insulin resistance (Banks 2004; Banks 2006;

Unger et al. 1991). At the level of the BBB, there is a tight relationship between the presence of insulin receptors and the topographic expression of glucose transporters particularly abundant in medial temporal lobe and diencephalic structures, which notably are related to neurocognitive functions (White 2002; Zhou et al. 2001), suggesting an important role of insulin in modulation of glucose uptake and utilization (Banks 2004; Baker et al. 2011; Craft et al. 2012; Hertz et al. 1981). Insulin stimulation of glucose transporter-4 (GLUT4) seems to be critical to the regulation of neuronal metabolism and the generation of energy needed for memory and other neurocognitive functions. The presence and functional activity of major insulin signal transduction molecules in human primary astrocytes has also been demonstrated, including glycogen formation and cell proliferation, thus supporting neurons with energy, since neurons cannot store glycogen for their own activity (Heni et al. 2011).

A growing body of evidence points to the importance of a condition of the insulin inability to serve its physiological function in the brain, in literature described by two alternative terms, "brain insulin resistance" (BIR) (Su et al. 2017; Talbot et al. 2012; de la Monte et al. 2012) or "insulin resistant brain state" (IRBS) (Correia et al. 2013; Frisardi et al. 2010; Plaschke et al. 2010a, b; Salkovic-Petrisic et al. 2009). At the molecular level, BIR is characterized by a reduced response to insulin signalling generally downstream the insulin receptor (IR)—insulin receptor substrate (IRS)—phosphatidyl inositol kinase-3 (PI-3) pathway in the brain, which, particularly considering the neurotrophic, neuroprotective, and neuromodulatory roles of brain insulin, may lead to neurodegeneration and cognitive impairment as seen in AD as well as metabolic alterations in hypothalamic functions, as seen in obesity and T2DM (Kullmann et al. 2016). Although some authors proposed that it might be considered as type 3 diabetes (de la Monte and Tong 2014), others strongly disagree (Talbot 2014; Talbot and Wang 2014). BIR actually represents a brain-related metabolic syndrome associated with metabolic and oxidative stresses and neuroinflammation in the brain, which may or may not be accompanied by alterations in peripheral metabolic homeostasis, since T2DM increases the risk for AD (and vice versa), but neither all T2DM patients develop AD (and vice versa) nor AD is necessarily associated with hyperglycemia (Talbot 2014; Talbot and Wang 2014; Blázquez et al. 2014).

A clinical study on 30 normal, 29 MCI, and 30 AD patients (Talbot et al. 2012) demonstrated that cognition was negatively associated with levels of candidate biomarker of BIR serin-phosphorylated insulin receptor substrate-1 (IRS-1 pS616) in the hippocampus, and that association of episodic memory and IRS-1 pS616 was statistically independent of Aβ plaques, suggesting that BIR is mechanistically closer than the plaques to the molecular causes of cognitive decline in AD. A very recent longitudinal, 35-month study in 57 MCI and 64 cognitively unimpaired controls confirmed the existence of the interaction between insulin resistance-related genetic polymorphisms (AKT2, PIK3CB, IGF1R, PIK3CD, MTOR, IDE, AKT1S1, and AKT1) and cognitive impairments in MCI subjects, providing in vivo evidence that pathway of BIR modifies cognitive performance, further showing that the influence occurred in the absence of diabetes (Su et al. 2017).

Insulin resistance impairs the normal activity of the brain; both experimental, imaginistic, and clinical non-interventional studies have identified correlations between insulin and cognitive functions—in particular impaired memory and AD but also increased insulin resistance in a significant number of patients with other neurodegenerative diseases (de Felice et al. 2014; Craft et al. 2012; de la Monte et al. 2012; Craft and Christen 2010; Rönnemaa et al. 2008; de la Monte et al. 2009). These implications could be related to the role of insulin in the normal APP and Aβ cellular synthesis and processing, but also in the brain-liver metabolic axis (de la Monte et al. 2012; de la Monte 2009; Banks et al. 2012; Craft et al. 2013; Gasparini and Xu 2003; Lin et al. 2000; Matsuzaki et al. 2010; Passafaro et al. 2001; Sagare et al. 2012; Tamaki et al. 2007; Lopez et al. 2011). The role of brain insulin in the control of the turn-over of Aβ is also important for mixed and vascular cognitive impairment as there is a tight interference between the brain vascular risk factors and Aβ (as recently stated by AHA/ASA based on a significant number of published research data) (Gorelick et al. 2011).

In addition, insulin has been shown to regulate the phosphorylation of tau proteins (Rudolph et al. 2016). Hyperphosphorylated tau contributes to the formation of neurofibrillary tangles (Kimura 2016). It is also reported that there are genomic/transcriptomic links between AD and DM by meta-analysis study (Mirza et al. 2014).

A neuropathological evaluation of glucose/insulin-related molecules in AD, DM and controls is presented in Table 1. These molecular post-mortem brain data agree with histological and clinical studies underlying the importance of glucose/insulin pathology as risk factors for cognitive dysfunction. These results point to a concomitant occurrence of alterations in the energy metabolism pathways.

Considering the dysfunction of the brain insulin system found in AD patients post-mortem (Luchsinger 2012), an experimental rat model, the STZ-ICV model, which mirrors an insulin resistant brain state, seems to be an appropriate animal model for AD (Salkovic-Petrisic et al. 2009; Luchsinger 2012; Hoyer 1998, 2004; Israili 2011; Grünblatt et al. 2007; de la Monte 2009).

Table 1 Neuropathological evaluation of glucose transporter, insulin/insulin receptor, and its related molecules in AD compared to T2DM and controls

Parameter	Pathological group (n)	Brain region	Results	Reference
O-GlcNAcylation GLUT3 Tau phosphorylation	Control ($n = 7$) T2DM ($n = 11$) AD ($n = 10$) T2DM + AD ($n = 8$)	Frontal cortices	↓ O-GlcNAcylation Glucose vs. Ct ↓ GLUT3 vs. Ct (higher extent in T2DM) ↑ Tau-p vs. Ct (in AD and in some tau epitopes in T2DM)	Liu et al. (2009)
Aβ plaques AGEs RAGE Tau	Control ($n = 9$) DM ($n = 3$) AD ($n = 10$) AD + DM ($n = 9$)	Cerebellum, hippocampus and cerebral cortex (temporal, frontal and parietal lobes)	↑ Aβ plaques vs. Ct and DM ↑ AGEs vs. Ct and DM ↑ RAGE vs. Ct (in particular in AD + DM) hilar cells ↑ Tau aggregates vs. Ct and DM (in particular in AD + DM)	Valente et al. (2010)
IRβ Phosphorylated PPARγ	Control ($n = 9$) AD ($n = 10$) T2DM ($n = 10$) AD + T2DM ($n = 10$)	Frontal cortex, dorsal and ventral hippocampus	↓ IRβ cortex vs. Ct, T2DM and AD + T2DM ↓ IRβ hippocampus vs. Ct ↑ p-PPARγ vs. Ct	Bartl et al. (2012)
Ceramide (activates insulin resistance)	Control ($n = 8$) Moderate AD ($n = 8$) Advanced AD ($n = 8$)	Anterior frontal lobe	↑ Ceramide in advanced AD	de la Monte et al. (2012)
Insulin stimulation → IR, IRS-1, PI3K, IGF-1R and IRS-2	Control ($n = 8$) AD ($n = 8$)	Cerebral cortex, hippocampal formation	↓ Insulin response IR, IRS-1, PI3K, IGF-1R and IRS-2 vs. Ct	Talbot et al. (2012)
IRβ-pY960 IRS1 IRS1-pY^{612} IRS1-pY^{941} IRS1-pY^{312} IRS1-pS^{616} IRS1-pS$^{636/639}$ PIP3 GSK3β mTOR-pS^{2448}	Control ($n = 30$) MCI ($n = 29$) AD ($n = 31$)	Hippocampal CA1	↓ IRβ-pY960 in AD ↓ PIP3 and GSK3β vs. Ct ↑ IRS1, IRS1-pS^{616} and IRS1-pS$^{636/639}$ vs. Ct ↑ IRS1-pY^{612}, IRS1-pY^{941}, IRS1-pY^{312} and mTOR-pS^{2448} in AD	Talbot et al. (2012)
Aβ HNE AGE Insulin GLP-1 PYY Leptin	Control ($n = 8$) Moderate AD ($n = 8$) Advanced AD ($n = 8$)	Frontal lobe	↑ Aβ and HNE in Advanced AD ↑ AGE vs. Ct ↓ Insulin, GLP-1 and PYY in advanced AD ↑ Leptin in advanced AD	Lee et al. (2013)
IRS1-pS^{616} IRS1-pS^{312} Akt-pS^{473}	Control ($n = 25$) AD (25) Tauopathy ($n = 38$) α-synucleinopathy ($n = 41$) TDP-43 proteinopathy ($n = 28$)	Midfrontal gyrus, angular gyrus, hippocampus	↑ In AD and slightly in tauopathies	Yarchoan et al. (2014)

Table 1 continued

Parameter	Pathological group (*n*)	Brain region	Results	Reference
IRS1-pS^{616} IRS1-pS$^{636/639}$ IRS1-pY^{612}	Control ($n = 3$) AD ($n = 3$)	Temporal cortex, hippocampus	↓ IRS1-pS^{616} nucleus stains vs. Ct ↓ IRS1-pS$^{636/639}$ nucleus stains vs. Ct ↓ IRS1-pY^{612} nucleus stains vs. Ct	Garwood et al. (2015)
Aβ Autophagy (Beclin-1 and LC-3) PI3K/Akt/mTOR Phosphatase Tensin homolog IRS1 GSK3β	Control ($n = 8$) Late AD ($n = 8$) Amnestic MCI ($n = 8$) PCAD ($n = 8$)	Inferior parietal lobule	↑ Aβ with ↓ autophagy vs. Ct ↑ PI3K/Akt/mTOR in MCI and AD vs. Ct ↓ Phosphatase and tensin in MCI and AD vs. Ct ↑ IRS1 and GSK3β in MCI and AD vs. Ct	Tramutola et al. (2015)

*GLUT*3 glucose transporter 3, *Ct* control, *AD* Alzheimer's disease, *T2DM* type 2 diabetes mellitus, *AGEs* advanced glycation end products, *RAGE* receptor for AGEs, *DM* diabetes mellitus, IRβ insulin receptor subunit β, *IRS*1 insulin receptor substrate-1, *MCI* mild cognitive impairment, *PCAD* pre-clinical AD, *HNE* 4-hydroxynonenal

Brain insulin resistance (BIR) as a shared pathological feature in obesity, cardiovascular disease, T2DM, and dementia

Evidence has gathered suggesting that BIR seems to be a shared pathological feature of metabolic and cognitive disturbances in T2DM, obesity, cardiovascular disease, and dementia patients (Kullmann et al. 2016; Lutski et al. 2017), which may provide the missing link between these disorders. Indeed, recent evidence suggests that insulin resistance is related to subsequent poorer cognitive performance and greater cognitive decline among patients with cardiovascular disease with and without diabetes (Lutski et al. 2017). Clinical investigation of the link between the obesity and BIR showed that obese men respond to cognitive but not to catabolic brain insulin signalling (Hallschmid et al. 2008), indicating that not all insulin activities in the brain have been equally affected by BIR and that insulin resistance in metabolic disorders does not uniformly affect all target cells and intracellular signaling pathways in the brain (Könner and Brüning 2012). Whereas dementia predominately affects cognitive target regions of insulin action, T2DM- and obesity-associated BIR predominately targets hypothalamic insulin action, but there is overlap of these three disorders in impairment of functional connectivity in prefrontal and lateral temporal cortices and hippocampus as reviewed by Kullmann et al. (2016). Thus, numerous clinical phenotypes may arise from selective insulin resistance, leading to inhibition of defined intracellular signaling pathways in some tissues, while in other cell types, insulin action is maintained or even overactivated (Könner and Brüning 2012). Furthermore, magnetoencephalographic studies on carriers of obesity- and diabetes-risk genes (fat-mass and obesity-associated gene/*FTO*/and *IRS-1*, respectively) showed an attenuated insulin-mediated response in the brain (Tschritter et al. 2006, 2007). In lean humans, insulin infusion modulates cerebrocortical activity as demonstrated by magnetoencephalography, while these effects are suppressed in obese individuals, indicating lower cerebrocortical response to insulin, i.e., BIR in this particular region, found in individuals with the Gly972Arg polymorphism in *IRS-1*, a T2DM risk gene (Tschritter et al. 2006). The same group demonstrated also that variation in the *FTO* gene locus (obesity-risk gene) is associated with cerebrocortical insulin resistance, but in these subjects, the effect of *FTO* polymorphism was independent of the Gly972Arg polymorphism in *IRS-1* (Tschritter et al. 2007). These studies clearly indicate that each genetic determinant for BIR involves different neuronal systems (Kullmann et al. 2016), which may provide an explanation why AD is associated with T2DM in some, but not all demented patients, and vice versa, why T2DM is associated with AD in some but not all diabetic patients.

BIR is not necessarily a secondary pathological event as mentioned earlier in the text (references Neumann et al. 2008; Kimura 2001, 2016; Craft et al. 1998; Craft and Watson 2004). Considering the BIR as a shared feature in obesity, T2DM, and dementia, etiology of BIR as a primary pathological event could be related to the maternal environment during pregnancy and its influence on the fetus, according to the studies showing that the change of insulin action in fetuses of diabetic mothers influences the fetal brain (Sobngwi et al. 2003). Intrauterine exposure of fetuses to a non-physiological concentration of insulin during critical periods of early development can lead to a permanent malprogramming of fundamental regulatory systems including those in hypothalamus, as demonstrated

for elevated insulin level during perinatal life which programmed the development of obesity and diabetes (Plagemann 2008). Recent meta-analysis of 19 studies including 2260 subjects has confirmed a strong support for the fetal programming hypothesis (Pearson et al. 2015). It is not only stress that might be a confounding factor, as the effects of chronic exposure to stress hormones on cognition at different stages in life including the prenatal age, depend on the brain areas that are developing or declining at the time of exposure (Lupien et al. 2009). Therefore, environmental factors and epigenetic mechanisms operating during pregnancy and postnatally may affect particular susceptibility genes and stress factors, consequently affecting brain development and causing respective diseases like AD and/or T2DM that manifest late in life when aging takes place and may become a trigger of desynchronization of biological systems (Salkovic-Petrisic et al. 2009).

Cerebral blood flow

Age-related dysfunction based on reduced capillary function declines in uptake of energy metabolites, amino acids, trophic factors, and other metabolic constituents, is of eminent importance in a variety of brain-related disorders (Kang et al. 2017; Bellou et al. 2017). T2DM favours such age-dependent dysfunction and potentiates energy loss in brain tissue. Therefore, aging eventually combined with stress, which per se exerts negative effects on T2DM, is both potential risk factors for AD (de Matos et al. 2017).

While under physiological conditions, compensatory mechanisms are able to keep the homeostasis of brain nutrition for a long time, chronic dysfunction finally will overcome compensatory functions leading to neuronal death.

Glucose-6-phosphate dehydrogenase plays a pivotal role in homeostatic redox control by providing reducing equivalents to glutathione, the major non-enzymatic cellular antioxidant. As OS plays an important role in the pathogenesis of AD, it is noteworthy that both glucose-6-phosphate dehydrogenase and sulfhydryl concentrations are upregulated in AD, showing compensatory regulation.

According to an alternative two-hit vascular hypothesis, Aβ accumulation in the brain is a second pathology (hit 2) initiated by vascular damage (hit 1; Fig. 1). Neurovascular dysfunction and hypoperfusion/hypoxia can reduce Aβ vascular clearance across the BBB and increase Aβ production from Aβ precursor protein (APP), respectively, causing Aβ accumulation in the brain. Elevated levels of Aβ in the brain may in turn accelerate neurovascular and neuronal dysfunction and promote self-propagation, leading to cerebral β-amyloidosis (Sagare et al. 2012).

Chronic brain hypoperfusion (CBH) can be present for many years without eliciting mental symptoms, creating instead an insidious neuronal energy crisis that is finally expressed by progressive cognitive deficits in affected individuals.

In this scenario, the presence of advanced aging plus vascular risk factors can lower cerebral perfusion by inducing any of number of abnormal hemodynamic mechanisms affecting blood pressure, vessel patency, vascular wall shear stress, blood flow resistance, blood viscosity, and chemical blood flow regulators (Blennow et al. 1990).

As neurons have no energy reserves, the performance of cognitive tasks is critically dependent on the steady delivery of adequate oxygen and glucose to produce adenosine triphosphate (ATP). This nutrient delivery is inadequate in the aging brain.

Diminished CBF, neurovascular dysfunction, and impaired vascular clearance of Aβ from brain support an essential role in linking DM and AD pathogenesis (de la Torre 2010).

The glymphatic system mediates clearance of the interstitial solutes in the brain by exchange of cerebrospinal and interstitial fluids (CSF and ISF). The glymphatic system consists of CSF influx from the paravascular space of cerebral arteries, ISF clearance along the para-venous space and the astroglial water channel AQP4 that partially mediates transparenchymal changes of CSF and ISF (Iliff et al. 2013; Yang et al. 2013). Impairment of the glymphatic system induces accumulation of Aβ (Iliff et al. 2013; Yang et al. 2013). Using a rat model of DM induced by nicotinamide and STZ, Jiang et al. (2016) showed that compared to age matched non-diabetic rats, middle-aged DM rats exhibited spatial learning deficits. An odour recognition test which detects non-spatial memory deficits showed that DM rats failed to form new memories. In vivo dynamic Gd-DTPA contrast-enhanced MRI analysis confirmed by ex vivo confocal image analysis indicated that DM impairs the glymphatic system that mediates clearance of the interstitial solutes in the brain (Jiang et al. 2017). Cognitive deficits were highly and inversely correlated to the impairment of the glymphatic system. Immunohistological analysis showed the presence of microvascular leakage and loss of AQP4, axons, and oligodendrocytes in the hippocampi of DM rats (Hamed 2017).

Inflammation in the diabetic brain

It has been shown clinically that disturbances of the BBB play a role in the development of AD, especially in elderly patients (Blennow et al. 1990). Therefore, peripheral inflammatory factors from DM could leak to the brain

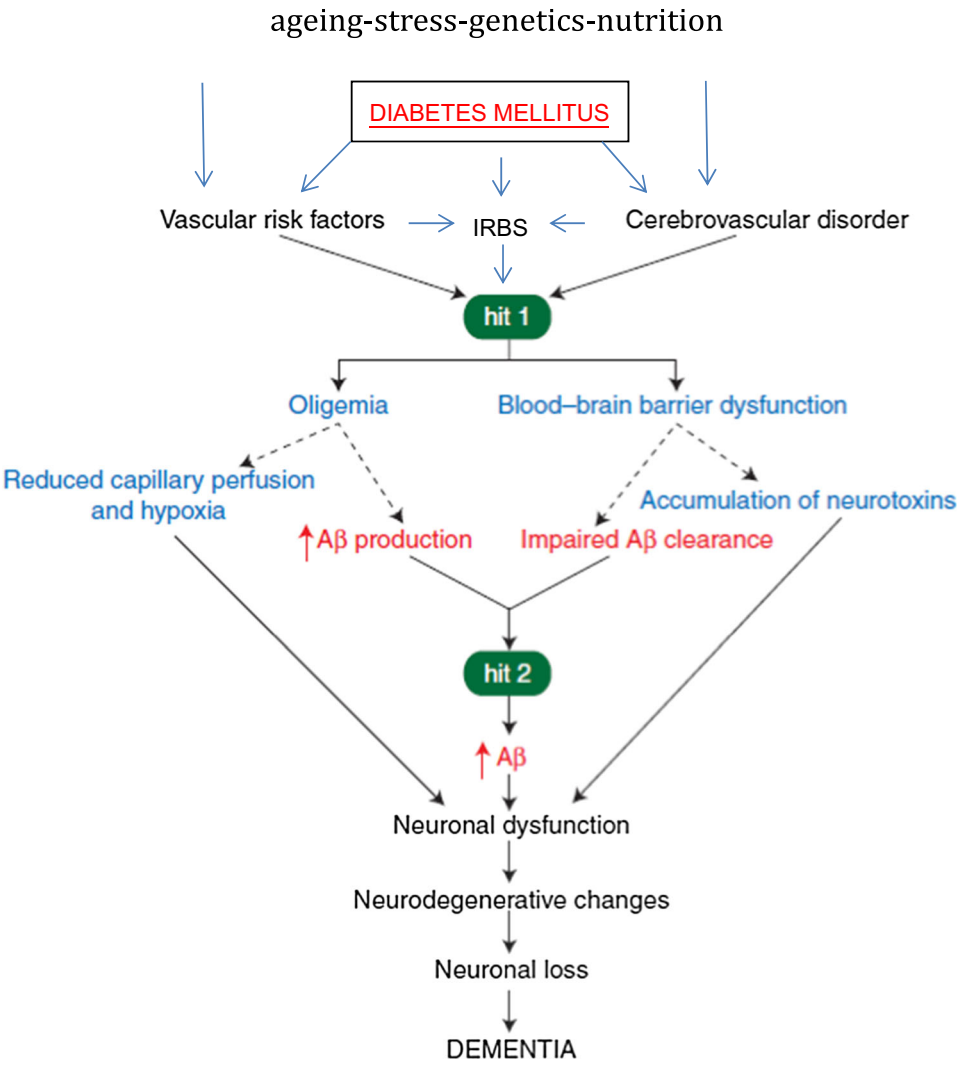

Fig. 1 Vascular hypothesis of Alzheimer disease. *HIT 1* Vascular damage as primary pathological event. *HIT 2* Aβ accumulation as secondary pathological event. Modified from Sagare et al. (2012) (This copyright agreement is admitted by describing Cold Spring Herb Perspect Med 2012;2:a011452)

parenchyma and induce activation of microglial cells to release inflammatory molecules (Breteler 2000), thus contributing to the pathophysiology of AD and VaD. There have been studies which have pointed out that inflammatory pathways may be acting as a possible mechanistic link between the two disorders. Takeda et al. (2010, AD and VaD) crossed transgenic mice (APP23) with diabetic mice (ob/ob) and looked at the metabolism and pathology of the brains in those double mutant mice (APP+-ob/ob). AD-like cognitive impairment was observed in APP+-ob/ob mice. Cerebrovascular inflammation, severe cerebral amyloid angiopathy, and up-regulation of RAGEs were observed in those double mutant mice even before the appearance of cerebral amyloid angiopathy, suggesting their role in cognitive impairment (Takeda et al. 2010). These findings agree with pathology of the cerebral vasculature in AD and DM (Blennow et al. 1990; Breteler 2000).

Oxidative stress (OS) caused by chronic hyperglycemia in chronic experimental diabetic neuropathy has been shown to cause oxidative injury of dorsal root ganglion neurons, specifically damaging the mitochondrial function and neuronal cell death (Schmeichel et al. 2003).

Prolonged metabolic stress conditions could be activated by various cell stressors, as hypoxia, oxidative stress, viral infections, and trophic withdrawal or various insults unveil deleterious effects of p53-evoked insulin resistance in neurons; enhancement of transcription of pro-oxidant factors, accumulation of toxic metabolites (AGE and ROS)-modified cellular components, together with activation of proapoptotic genes, could finally move a suicide death program of autophagy/apoptosis in neurons. The important role of p53 driving insulin resistance in AD brains validates attempts to inhibit p53 activity in neurons, since it could promise an improvement of the disease therapy. Recent studies reveal the impact of p53 on expression and processing of several microRNA (miRs) under DNA damage-inducing conditions. In addition, the role of miRs in promotion of insulin resistances and in T2DM has been well documented. Detailed recognition of the role of p53/miRs

crosstalk in driving insulin resistance in AD brains could improve the disease diagnostics and future therapy (Vousden 2010).

The kynurenine pathway, the main metabolic route of tryptophan degradation, produces several neuroactive molecules [such as the excitotoxin antagonist kynurenic acid (KYNAC) and the excitotoxin quinolinic acid (QA)]. Alterations in the kynurenine pathway may promote glutamate-mediated excitotoxic neuronal damage and inflammatory processes (Vecsei et al. 2013). Recently, it was shown that STZ-induced experimental T1DM increases hippocampal content of KYNAC (Chmiel-Perzynska et al. 2014). The increased KYNAC level may have negative impact on cognition. KYNAC in the course of DM could be associated with an enhanced ketone body formation. In cortical slices and glial cultures, beta-hydroxybutyrate (BHB) augments KYNAC production by stimulating KATs activity in the protein kinase-A dependent way, thus explaining the neuroprotective actions of BHB (Chmiel-Perzynska et al. 2011).

Potential role of butyrylcholinesterase in linking diabetes and cognitive dysfunction

In AD, the brain levels of AChE go down, while those of BChE (the protein butyrilcholinesterase) go up, resulting in a dysregulation causing cholinergic deficit. As levels of that enzyme are altered in T2DM too, those authors suggest a synergistic negative interaction of T2DM and AD on cholinergic neurotransmission (Mushtaq et al. 2014). Among common pathogenic factors between DM and AD, BChE has been studied in vitro and in plasma (Sridhar et al. 2006; Rao et al. 2007; Shaikh et al. 2014). Alterations in the level of plasma BChE occur in DM; variant forms of the plasma enzyme occur in both DM and AD (Sridhar et al. 2010; Raygani et al. 2004). In vitro studies demonstrate a common pathogenic mechanism (Sridhar et al. 2006; Diamant et al. 2006). Whereas brain hyperglycemia mediates hippocampal neuron responses (Macauley et al. 2015), BCHE levels also correlate with cerebral glucose metabolism and cerebral Aβ load (Darreh-Shori et al. 2011). BChE associates particularly with the malignant form of Aβ plaques, suggesting its role in transforming non-fibrillar to the malignant fibrillar form (Reid and Darvesh 2015). To account for a gender difference, a gene–gene interaction between BChE and estrogen-associated genes was proposed (Reid and Darvesh 2015). However, the relation between BChE and AD is not settled yet. While an earlier meta-analysis of the K-Variant of BChE suggested that it was related to development of AD in Asians (Want et al. 2015), but a more comprehensive meta-analysis failed to confirm the relation (Ji et al. 2015).

T2DM is not only associated with an increased risk of cognitive decline and different types of dementia but also with cerebrovascular and peripheral vascular disease (Hoyer et al. 1999; Hoyer 1998, 2004; Israili 2011). Moreover, cerebrovascular disease may contribute to the severity of cognitive decline in AD (Last et al. 2007).

For the group, it is evident that disruption of glucose metabolism in both AD and VaD is based on multiple triggers. However, there is no agreement on follow-up and time-course of pathological cascade.

Imaging the diabetes–cognitive impairment relationship

Rapid advances in neuroimaging have confirmed a link between cognitive impairment and poor metabolic control in DM, mediated by the structural and functional brain changes (van Bussel et al. 2017). Whole-brain analysis revealed a consistent link between DM and brain atrophy and this atrophy is often more pronounced within the hippocampus (Gold et al. 2007). However, a pooled analysis of three cohort studies showed that the degree of hippocampal atrophy in T2DM is comparable to the degree of total brain atrophy (Biessels et al. 2006a, b). Brain atrophy in T2DM is associated with poor cognition, predominantly attention and executive function, and information-processing speed and memory (Moran et al. 2013; van Elderen et al. 2010; Manschot et al. 2006).

Whole-brain grey matter (GM) atrophy may be associated with T2DM; the association is more convincing for regional GM atrophy (Gold et al. 2007; Last et al. 2007). Similarly, the association of global and regional white matter (WM) atrophy and WM hyperintensities with DM was not consistently reported (Friedman et al. 2014). T2DM is clearly associated with the occurrence of lacunes (van Harten et al. 2007).

Functional magnetic resonance imaging (fMRI) demonstrated reduced synchronized activity within default mode network in cognitively normal T2DM patients (Musen et al. 2012). Regional basal cerebral blood flow (CBF) and cerebrovascular reactivity (CVR) have been shown to be decreased in T2DM patients (Zlokovic 2008). Longitudinal studies have confirmed the association of CBF and CVR with cognitive function and total brain volume in T2DM at baseline. However, both indexes of cerebral hemodynamics have not been predictive for atrophy and cognitive decline, and seem to be secondary phenomena (Brundel et al. 2012).

Neuroimaging studies may serve as early biomarkers and as monitors of progression of cognitive impairment in subjects with DM (Moran et al. 2015). Several methods

have been attempted to identify anatomical and biomolecular markers linking accelerated cognitive decline with insulin resistance. First, MRI studies have consistently shown that chronic hyperglycemia is associated with brain atrophy and cerebrovascular lesions (Moran et al. 2013; van Bussel et al. 2017), which are hallmarks of attention deficits and impaired executive functioning (McCrimmon et al. 2012). There is no consensus on the exact mechanism of neurodegeneration leading to accelerated cognitive decline in DM and whether it is mediated by neuronal atrophy or/and cerebrovascular lesions (Biessels 2013). Such uncertainty undermines MRI as an early predictive tool for the transformation potential of MCI into AD in normal as well as DM subjects. For example, the AD Neuroimaging Initiative (http://www.adni-info.org/) has been validating the use of MRI/PET imaging for the prediction of MCI-to-dementia conversion within 18 months of diagnosis. Patients who converted to dementia showed changes in GM volume, amyloid deposition, and glucose metabolism in multiple regions compared with those who did not develop dementia. In a recent analysis of the data collected using structural MRI, amyloid-PET and 18F-FDG-PET scans, investigators could predict the transition with maximum accuracy of 72% (Teipel et al. 2015). In addition to its low predictive potential, this approach can only provide circumstantial clues on the underlying mechanism of accelerated cognitive decline leading to AD and dementia in DM patients.

In addition, DM triggers molecular alterations that elicit deranged microvascular and mitochondrial functions, increased inflammation, and elevated levels of advanced glycation end products (AGEs) (Kim et al. 2012; Goldin et al. 2006). All these diverse pathways converge at a nodal point where positive feedback loops exacerbate OS which is invariably implicated in neurotoxicity, neurodegeneration, and cognitive deficits. It can be suggested, therefore, that biomarkers of OS may provide early predictive probes for cognitive decline in DM subjects (Praticò et al. 2000, 2002; Keller et al. 2005; Aluise et al. 2011; Baldeiras et al. 2010; Thomas et al. 1996).

The group concluded that imaging studies (MRI, PET) contribute to an early diagnosis of AD and VaD. However, specificity and selectivity do not reach sufficient levels to be used solely for a precise clinical diagnosis.

Pathology

Both T1DM and T2DM induce regional microstructural changes in cortical and subcortical brain structures that are associated with impairment of neurocognitive functions (Seaquist 2015). Some autopsy studies stated that patients with DM have significantly less AD pathology but more frequent cerebrovascular lesions including microvascular changes (Alafuzoff et al. 2009; Beeri et al. 2005; Nelson et al. 2009; Ahtiluoto et al. 2010) or both types of cerebral pathology (Alafuzoff et al. 2009; Vagelatos and Eslick 2013; Ahtiluoto et al. 2010; Takeda et al. 2011; Verdile et al. 2015), and white matter lesions (Jellinger 2015a, b). The increased risk of cognitive decline in elderly subjects with DM is due to dual pathology, involving both the CVD and cortical atrophy (Biessels et al. 2006a, b; Umegaki 2012). Two different patterns of cerebral injury were seen in patients with dementia depending on DM status: greater amyloid plaque load in untreated DM patients but more frequent deep microvascular infarcts in those with treated DM (Sonnen et al. 2009). Central vascular disease and exacerbated pathology were seen in a mixed model of DM and AD by crossing APP/PS1 mice (AD model) with db/db mice (DM model) that show an age-dependent synergistic effect between DM and AD, including brain atrophy, senile plaques, hemorrhagic burden, and increase of microglia activation (Ramos-Rodriguez et al. 2015). Insulin resistance, hyperinsulinemia, and hyperglycemia can promote the onset of AD (Rönnemaa et al. 2008; de Oliveira Lanna et al. 2014) by accelerating tau phosphorylation and neuritic plaque formation (Bitel et al. 2012; Matsuzaki et al. 2010) and, overlapping with AD pathology, aggravate the progression of neurodegeneration due to OS, mitochondrial dysfunction, neuroinflammation, etc. as a common background (Carvalho et al. 2015; Kraska et al. 2012; Roriz-Filho et al. 2009; Rosales-Corral et al. 2015). Thus, impaired insulin signaling may be a possible link between AD and DM (Jellinger 2015a, b; Sato et al. 2011). Although insulin mitigates Aβ deposition and phosphorylation of tau (Bedse et al. 2015), DM in combination with APOEε4 may lead to excessive hyperphosphorylation of tau (Matsuzaki et al. 2010) and exacerbation of AD pathology (Malek-Ahmadi et al. 2013). However, a very recent publication (Abner et al. 2016) concludes that diabetes is associated with cerebrovascular but not AD pathology.

An extensive literature search reviewing 275 publications reporting post-mortem brain analyses of AD and VaD and published between 1980 and 1994 was performed (Gsell et al. 1996). In comparison to AD, in VaD, human brain neurotransmitter alterations are mild, e.g., for choline acetyltransferase activity, muscarinic receptor density, serotonin, dopamine, homovanillic acid, dopamine D1-and D2-receptor density, noradrenaline, and gamma aminobutyric acid (GABA), while 5-hydroxyindoleacetic acid (5-HIAA) shows a more pronounced deficiency. This data summarized here agree in principle with more recent conclusions of post-mortem human brain studies and experimental models (Ohara et al. 1994; Pimlott et al.

2004; Jia et al. 2004; Tohgi et al. 1996; Chen et al. 2013; Lee et al. 2014; Niwa et al. 2002; Pedrós et al. 2014; Knezovic et al. 2015; Barilar et al. 2015). CSF concentrations of choline were significantly higher in VaD patients compared to AD and controls but did no correlate with mini-mental state examination (MMSE) scores (Jia et al. 2004; Tohgi et al. 1996).

It is evident for the group that the pathology of AD and VaD shows multiple alterations at both neuropathological and neurochemical levels. In addition, mixed-type dementia pathology is frequent.

Animal models

There are few literature data on brain insulin resistance (BIR) and glucose hypometabolism in widely exploited transgenic AD mice models in which amyloid/tau-related gene manipulation is an inevitable starting point as antecedent to BIR allowing thus no clear conclusion on BIR–cognition relationship (Chen et al. 2013; Lee et al. 2014; Niwa et al. 2002; Pedrós et al. 2014), which contrasts animal treated intracerebroventricularly with STZ (non-transgenic STZ-icv model). STZ-icv administration induces dysfunctional insulin receptor signalling and mirrors the etiology of AD and in part that of cerebrovascular diseases (Table 2). Two long-term follow-up studies of STZ-icv rat model which provided the first staging of cognitive, structural/ultrastructural, neuropathological, and BIR markers in the STZ-icv rat model showed that cognitive deficit correlated well with GSK-3β activity (larger deficits–higher activity) and IDE protein expression (larger deficits–lower expression), in a bi-phasic time-dependent manner, with cognitive deficits becoming manifested later than dysfunctions in brain insulin system (Knezovic et al. 2015; Barilar et al. 2015). AD-like structural pathology seen in STZ-icv rat model in the form of early neurofibrillary changes and Aβ accumulation becomes manifested later than insulin- and memory-related changes and follows slow, graduating progression (Knezovic et al. 2015). Findings in this non-transgenic sAD animal model strongly support clinical data indicating BIR as a possible primary pathological event in AD development. Furthermore, recently developed and thus far less explored STZ-icv mokey model demonstrates BIR (Lee et al. 2014) accompanied by Aβ deposition and tauopathy (Yeo et al. 2015), while BIR induced by STZ-icv treatment aggravates cognitive deficits and increases the formation of pathomorphological AD hallmarks, particularly Aβ accumulation in APP overexpressing (Plaschke et al. 2010a, b) and Presenilin-1-Val97Leu mutant (Lin et al. 2014) transgenic mice AD models.

Long-term drug testing polygon considering the preliminary data of the therapeutic role of icv insulin in the STZ-icv model (Shingo et al. 2013) and of intranasal insulin in AD patients (Claxton et al. 2015) should be performed to elucidate the importance of glucose/insulin pathology as risk factor for both, AD and VaD.

The representative experiments (≥3 mg/kg STZ-icv; rat) demonstrate the following order of AD-like pathology appearance: IRBS = oxidative stress = neuroinflammation > glucose hypometabolism = tau pathology = cognitive deficits > amyloid β1-42 accumulation > amyloid angiopathy > amyloid plaques. These data support possible causal role of IRBS in sAD etiopathogenesis (Chen et al. 2014; de la Monte et al. 2014), confirmed by therapeutic effect of icv insulin in this model (Shingo et al. 2013) and intranasal insulin in AD patients (Claxton et al. 2015), and contributing role of vascular pathology in progression of cognitive decline as demonstrated in 9-month follow-up studies of this model (Knezovic et al. 2015; Salkovic-Petrisic et al. 2011).

IRBS is a condition characterized at the molecular level by reduced response to insulin signaling downstream the insulin receptor (IR)–insulin receptor substrate (IRS)–phosphatidyl inositol kinase-3 (PI-3) pathway in the brain, which, particularly considering the neurotrophic, neuroprotective and neuromodulatory role of brain insulin (Craft and Christen 2010; Gasparini and Xu 2003; Sato et al. 2011), may lead to neurodegeneration and cognitive impairment as seen in AD. Although sometimes termed "type 3 diabetes" (de la Monte and Tong 2014), it actually represents a brain-related metabolic syndrome associated with metabolic and oxidative stress and neuroinflammation in the brain, which may or may not be accompanied by alterations in peripheral metabolic homeostasis, since T2DM increases the risk for AD (and vice versa), but neither all T2DM patients develop AD (and vice versa) nor AD is necessarily associated with hyperglycemia (Talbot and Wang 2014; Talbot and Wang 2014; Blázquez et al. 2014).

While animal models are referred to in other consensus BMC-related manuscript, the group focused here on modelling the IRBS. It is concluded that the icv STZ rodent model mirrors AD and VaD pathologies in many respects. The model should be used with or without combination of transgenic mouse models.

Treatment of diabetes-related cognitive impairment

Currently little is known regarding the effect of diabetes interventions on diabetes-related cognitive impairment. The ACCORD-MIND study conducted among ~3000

Table 2 Cerebral amyloid angiopathy in the rat model of sporadic Alzheimer's disease (sAD) induced by intracerebroventricular administration of streptozotocin (STZ-icv) which generates insulin resistant brain state (IRBS) and dose- and time-dependent AD-like pathology

AD-like pathology in rat	Time after ≥3 mg/kg STZ-icv treatment (months)				
	<0.5	≥0.5	≥1	≥3	≥6
Cognitive deficit	− Knezovic et al. (2015)	+ Knezovic et al. (2015), Agrawal et al. (2011)	+ Knezovic et al. 2015, Kosaraju et al. (2013)	+ Knezovic et al. (2015), Hoyer et al. (1999), Samy et al. (2016)	+ Knezovic et al. (2015)
Tau pathology	ND	+ Knezovic et al. (2015), Barilar et al. (2015), Deng et al. (2009a, b), Lester-Coll et al. (2006)	+ Knezovic et al. (2015), Barilar et al. (2015), Kumar et al. (2010), Lester-Coll et al. (2006)	+ Knezovic et al. (2015), Barilar et al. (2015)	+ Knezovic et al. (2015), Barilar et al. (2015)
Amyloid β1-42 accumulation	− Knezovic et al. (2015)	− Knezovic et al. (2015)	−/+ Knezovic et al. (2015), Correia et al. (2013), Kosaraju et al. (2013)	+ Knezovic et al. (2015); Samy et al. (2016)	+ Knezovic et al. (2015)
Amyloid β1-42 plaques	− Knezovic et al. (2015)	− Knezovic et al. (2015)	− Knezovic et al. (2015)	− Knezovic et al. (2015), Samy et al. (2016)	+ Knezovic et al. (2015)
Amyloid angiopathy	ND	ND	− Salkovic-Petrisic et al. (2011)	Salkovic-Petrisic et al. (2011)	Salkovic-Petrisic et al. (2011)
Insulin receptor signalling pathway dysfunction	+ Barilar et al. 2015	+ Barilar et al. (2015), Sharma and Gupta (2003), Agrawal et al. (2011), Lester-Coll et al. (2006)	+ Barilar et al. (2015), Du et al. (2014)	Barilar et al. (2015)	+ Barilar et al. (2015)
Glucose hypometabolism	ND	+ Hoyer and Lannert (2007), Plaschke and Hoyer (1993)	+ Hoyer and Lannert (2007), Plaschke and Hoyer (1993)	ND	ND
Cholinergic deficit	ND	+ Kumar et al. (2010), Tota et al. (2012)	+ De la Monte et al. (2006), Sharma et al. (2010)	ND	ND
Oxidative stress	+ Shoham et al. (2007), Hassanzadeh et al. (2015)	+ Shoham et al. (2007), Sharma and Gupta (2003), Javed et al. (2012)	+ Shoham et al. (2007)	+ Deng et al. (2009a, b), Samy et al. (2016)	ND
Neuroinflammation	+ Shoham et al. (2007), Deng et al. (2009a, b)	+ Shoham et al. (2007), Rodrigues et al. (2009)	+ Shoham et al. (2007)	ND	ND

STZ-icv streptozotocin-intracerebroventricularly, *AD* Alzheimer's disease, *ND* no data

\+ Change reported

− No changes found

+/− Inconsistent reports with changed or unchanged parameter

individuals with DM demonstrated that tight glycemic control significantly reduced the rate of brain atrophy over a period of 20–40 months compared with the standard glucose treatment; however, there was no difference between the groups in the rate of cognitive decline as measured by 4 cognitive instruments (Cukierman-Yaffe et al. 2009).

Analogue compounds for the incretin hormone GLP-1 (glucagon-like peptide-1), which facilitate endogenous insulin release and are used to treat T2DM, reduce Aβ accumulation, and rescue impairments in hippocampal synaptic plasticity and spatial learning memory in transgenic mouse models of AD (Gengler et al. 2012).

Many studies suggest that adding more insulin to the brain would improve memory and prevent cell damage (Shingo et al. 2013; Claxton et al. 2015). In individuals without DM, it has been shown amongst cognitively intact and cognitively impaired individuals that a form of insulin that enters the brain selectively has beneficial effects on some cognitive domains (Shemesh et al. 2012). In the ORIGIN cognitive sub-study, treatment of people with DM and prediabetes for 6.5 years with basal insulin had a neutral effect on cognitive function (Cukierman-Yaffe et al. 2014).

There is one interesting report on the use of bacteriophage as a common divergent therapeutic approach for treating AD and T2DM (Sohrab et al. 2014). Invokana (Canagliflozin), which has dual inhibitory effect on acetylcholinesterase as well as on SGLT2, represents advancement in the parallel management of AD and T2DM (Rizvi et al. 2014). Galangin (a novel natural ligand) has inhibition characteristics on human brain acetylcholinesterase, butyrylcholinesterase, and 5-lipoxygenase (Shaikh et al. 2014). Molecular interaction of human brain acetylcholinesterase (target enzyme in AD therapy) has also been studied with a natural inhibitor, Huperzine-B (Alam et al. 2014a).

Elements such as magnesium play an important role in the normal functioning of many enzymatic activities. There has been some evidence for the role of magnesium in the prevention and therapy of AD and T2DM (Gröber et al. 2015), and there are some recent nanotechnological approaches in the management of AD and T2DM (Alam et al. 2014b).

Pantethine has beneficial effects in vascular disease, is able to decrease the hyperlipidemia, moderates the platelet function, and prevents lipid-peroxidation (Horváth and Vécsei 2009). The disulfide group (oxidized form of pantethine) is necessary to lower the platelet response to activation by thrombin and collagen (Penet et al. 2008). It was found that orally active multifunctional antioxidants including pantethine delay cataract formation in streptozotocin T1DM and gamma-irradiated rats (Randazzo et al. 2011). Pantethine should be considered for the treatment of lipid abnormalities also in patients at risk such as those with DM and other dementia disorders.

The possible implications of the relationship between dementia/cognitive impairment and diabetes on the care of the older individual with diabetes

Current guidelines for treatment of individuals with DM include extensive life style changes in diet, physical activity, smoking cessation, medication, and routine medical follow-up (Powers et al. 2015). To successfully manage self-care of such changes, the individual with DM is required to have intact cognitive function; i.e., to understand and learn new information, memorize it, apply new behaviors and procedures, and make complex decisions in a changing environment. However, current DM treatment and surveillance do not include routine assessment of cognitive function and the cognitive function of the individual is not taken into consideration when devising a treatment plan. This is especially important when treating older people with DM, since DM and aging are both independent risk factors for cognitive dysfunction. In the face of increasing numbers of older people with DM the fact that cognitive impairment is another complication of DM has two important implications. One is that it is pivotal that the effect of currently used glucose lowering agents on this complication be understood. Second, cognitive assessment, i.e., screening and surveillance should be part of the routine care of the older person with DM.

Cognitive dysfunction can potentially present new barriers to self-care and to achieving glycemic control. Indeed, population studies have shown that among people with DM lower cognitive function was associated with worse efficacy of treatment indices such as glucose control (Cukierman-Yaffe et al. 2009) and a greater risk for incident hypoglycemia (Punthakee et al. 2012). Reciprocal associations are assumed between DM self-care, glycemic control, micro and macro vascular outcomes, and cognitive impairment. Indeed, in a sample of 1398 older community-dwelling adults with DM, as cognitive impairment worsened, so did participants' adherence to each diabetes self-care task with incremental increases in DM comorbidity (Esmaeili et al. 2016). In a population-based study, amongst ~3000 middle-aged individuals with diabetes, those with lower cognitive scores had a higher risk for hypoglycemia events that required the help of another (a possible sequel of poor self-care management skills as it requires the patient to be self-alert and active in the management of the disease) (Punthakee et al. 2012). Another study reported that providing memory strategies improved adherence to medication amongst elderly DM patients (Vedhara et al. 2010). Finally, a recent study reported that

in individuals with DM, lower executive function was associated with higher need of outpatient care.

Current guidelines for treating older people with DM recommend routine screening for cognitive dysfunction (Kirkman et al. 2012; Sinclair et al. 2015). However, cognitive dysfunction is only the tip of the iceberg of a continuum of cognitive decline which is accelerated in people with DM. Thus, it is also important to characterize the cognitive profile of the intact individual with DM enabling care takers to adapt the treatment plan according to the individual's cognitive capacities. Indeed, in the past 3 years at the Center for Successful aging with Diabetes at the Sheba Medical Center, Israel, we have been conducting multi-disciplinary evaluation that include extensive neuropsychological testing and evaluation of the medical, functional, and physical status of the older person with DM, followed by cognitively adapted tailor-made recommendations (including the use of cognitive rehabilitation strategies) and a follow-up plan that takes into consideration the cognitive profile of the individual. Participants have reported a significant improvement in quality of life. We hypothesize that this type of approach which includes cognitive screening, surveillance, and rehabilitation will improve the self-care capacity of the older individual with DM, thus improving glucose control and reducing the risk for DM complications and possibly reducing the accelerated rate of cognitive decline this population experiences.

When deciding which drug to add to the regimen of an older individual with DM, the potential risk for hypoglycemia with this agent should be evaluated. Hypoglycemia unawareness is very common in elderly DM patients. A study involving T2DM patients over 65 years of age and using continuous glucose monitoring revealed hypoglycemic episodes in as many as 80% of patients, including 56% with severe hypoglycemic episodes (<40 mg/dl), and none of these episodes were actually "felt" by a patient (Kagansky et al. 2003; Zoungas et al. 2010; Whitmer et al. 2009; Sinclair et al. 2011; Kasiukiewicz et al. 2015; Tseng et al. 2014). Thus, the type of glucose lowering agent chosen should take into consideration hypoglycemia unawareness as well as the cognitive profile of the older person with diabetes choosing therapy that is safer in this respect such as metformin, alpha-glucosidase inhibitors, thiazolidinediones, GLP-1 receptor agonists, DPP-4 inhibitors, SGLT-2 as opposed to insulin, sulfonylureas, or glinides (Chamberlain et al. 2016).

Differences between treated and not treated DM2 patients

T2DM patients may be treated with oral antidiabetic agents [such as sulfonylurea, metformin and dipeptidyl peptidase 4 inhibitor (DPP-4I)], insulin, or by diet control only. Although all treatments may reduce glucose level, which type of treatment is helpful in reducing the cognitive impairment, is not clear.

Early studies suggest that cognitive decline may be slower, if T2DM patients are treated with insulin instead than oral antidiabetic agents. Therapy with insulin may lower neuritic plaque density in hippocampus and other brain areas (Beeri et al. 2008). In addition, Plastino et al. demonstrated slower cognitive decline in T2DM patients with AD treated with insulin in comparison to patients treated with oral antidiabetic agents (Plastino et al. 2010). However, this relationship may not be straight forward. In a recent study, Herath et al. followed T2DM patients for 4 years and found no significant differences between patients from diet only, oral antidiabetic agents, and insulin groups (Herath et al. 2016).

New research shows that treatment with DPP-4 inhibitors (DPP4I) is helpful. Rizzo et al. demonstrated in a prospective 2-year study that patients treated with DPP4I and metformin had better cognitive functioning in comparison to patients treated only with sulphonyl urea and metformin (Rizzo et al. 2014). Similar results were found in a shorter study, where they followed patients for 6 months (Isik et al. 2017). T2DM patients with AD and without AD treated with DPP-4I performed better on MMSE 6 months after they started with the treatment than patients taking metformin (Isik et al. 2017). In addition, patients treated with insulin or DPP-4I also had better glucose control and lower HbA1c at the end visit.

Future strategies

Increasing evidence suggests that the production of new neurons in the adult hippocampus (adult neurogenesis; AN) plays an important role in different subtypes of learning processes and memory formations (Deng et al. 2009a, b) and seems also to contribute to cognitive flexibility (Burghardt et al. 2012). Indeed, hippocampal AN was demonstrated to be diminished in these icv STZ rats after 3 months (Sun et al. 2015).

Therefore, it has been suggested that altered AN in the hippocampus plays a role in the etiopathology of neurodegenerative disorders such as AD (for review, see Winner and Winkler 2015) and vascular dementia (Ekonomou et al. 2011). Cerebrovascular functions and AN both decline during aging (Kalaria 2009; Kempermann 2015) which stands to reason as AN occurs within an angiogenic niche (Palmer et al. 2000). Improved energy supply in experimental AN studies show improved AN when using DM related therapeutic strategies (Luitse et al. 2012; Biessels 2013; Sonnen et al. 2009; Jia et al. 2004; Tohgi et al. 1996; Chen et al. 2013; Lee et al. 2014; Niwa

et al. 2002), indicating an important role of glucose/energy supply for the proper integrity of AN physiology.

Conclusion

In many individuals, AD and VaD show an underlying pathology of glucose utilization based on a disturbance of insulin-related pathology, leading to a brain insulin resistance state. However, the risk factors rather induce a mechanisms independent from pathological mechanisms underlying AD and VaD. In fact, these probably have different causality, which is reflected in the prevalence/incidence of AD (about 60%) and VaD (about 20%) of all dementia disorders. Considering the brain insulin resistance as a shared pathological feature of T2DM and dementia which, most probably are a consequence of environmental factors and epigenetic mechanisms operating during pregnancy and postnatally may be manifested as one or the other disorder, T2DM contributes to disease onset and progression of both AD and VaD. Therefore, therapeutic strategies focusing on DM should be considered already in early stages of AD and VaD. Future strategies including AN may enlarge the therapeutic armamentarium. More focus should be put on delaying dementia onset in people with diabetes and on the challenges cognitive impairment imposes on the self-care capacity of this population.

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