

Encephalopathies: the emerging diabetic complications

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Abstract Diabetic encephalopathies are now accepted complications of diabetes. They appear to differ in type 1 and type 2 diabetes as to underlying mechanisms and the nature of resulting cognitive deficits. The increased incidence of Alzheimer's disease in type 2 diabetes is associated with insulin resistance, hyperinsulinemia and hyperglycemia, and commonly accompanying attributes such as hypercholesterolemia, hypertension and obesity. The relevance of these disorders as to the emergence of dementia and Alzheimer's disease is discussed based on epidemiological studies. The pathobiology of accumulation of β -amyloid and tau the hallmarks of Alzheimer's disease are discussed based on experimental data. Type 1 diabetic encephalopathy is likely to increase as a result of the global increase in the incidence of type 1 diabetes and its occurrence in increasingly younger patients. Alzheimer-like changes and dementia are not prominently increased in type 1 diabetes. Instead, the type 1 diabetic encephalopathy involves learning abilities, intelligence development and memory retrieval resulting in impaired school and professional performances. The major underlying component here appears to be insulin deficiency with downstream effects on the expression of neurotrophic factors, neurotransmitters, oxidative and apoptotic stressors resulting in defects in neuronal integrity, connectivity and loss commonly occurring in the still developing brain. Recent experimental data emphasize the role of impaired central insulin action and provide information as to potential therapies. Therefore, the underlying mechanisms resulting

in diabetic encephalopathies are complex and appear to differ between the two types of diabetes. Major headway has been made in our understanding of their pathobiology; however, many questions remain to be clarified. In view of the increasing incidence of both type 1 and type 2 diabetes, intensified investigations are called for to expand our understanding of these complications and to find therapeutic means by which these disastrous consequences can be prevented and modified.

Keywords Type 2 diabetes · Insulin resistance · Alzheimer's disease · Type 1 diabetes · Insulin deficiency · Encephalopathy

Introduction

The increasing incidence of type 2 diabetes mellitus (T2DM), particularly in developing countries, is well known. Probably less well known is the increasing incidence of type 1 diabetes mellitus (T1DM) with onset at increasingly younger ages. Both types of diabetes are associated with serious secondary complications affecting kidney, retina, peripheral nerve and the vasculature.

Recently, central nervous system complications (diabetic encephalopathies) are being increasingly recognized [1]. As in the other so-called microvascular complications, some of the underlying pathogenetic mechanism appear to be different in the encephalopathies of the two types of diabetes and the nature of cognitive deficits differ.

The relationship between diabetes and cognitive dysfunction was already proposed in 1922 [2]. In the last two decades, several studies have addressed the relationship between type 2 diabetes mellitus (T2DM) and cognition [3–8]. Population-based studies generally show a lower

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score on cognitive screening tests like the Mini-Mental State Examination (MMSE) in T2DM patients than in non-diabetic patients matched for age, sex and education [9–11]. Additional longitudinal studies show an accelerated decline in cognitive function over time in diabetic patients [12, 13]. The cognitive domains that appear to be predominantly affected include attention, processing speed and memory [14]. Also, pre-diabetic stages with hyperinsulinemia but without established diabetes [15], and metabolic syndrome with hypertension, dyslipidemia and obesity show worse cognitive performances [16] and increased rates of decline over time [17]. Both diabetes and metabolic syndrome are associated with increased risks for micro- and macro-vascular disease and cerebrovascular accidents with compounding effects on cognitive deficits [18]. Metabolic syndrome alone without diabetes per se predisposes to Alzheimer's disease (AD) [19]. With respect to T2DM, there are now multiple studies showing an increased incidence of dementia [3–5], although it is not clear what roles the underlying mechanisms, such as hyperglycemia, hyperinsulinemia, impaired insulin signaling and associated innate inflammation, may play. They will be discussed in detail.

T1DM affects brain function and brain structure in children. Diabetic children are more likely to perform poorly in school than their non-diabetic classmates and show decreased intelligence and academic achievements. Children diagnosed with T1DM before the age of 6 [20], at a time when the brain is still developing [21], are particularly vulnerable showing impaired results on cognitive tests, affecting memory and learning abilities. Studies of brain function and structural neuroimaging have demonstrated associated anomalies.

In T1DM, earlier studies associated these cognitive shortcomings with repeated episodes of hypoglycemia. However, recent studies have not confirmed such an association [22, 23]. There is evidence suggesting that elevated blood glucose level is a contributing factor. Recent clinical data as well as experimental findings suggest that the initial insulin and C-peptide deficiencies play dominant roles in the development of T1DM encephalopathy [24, 25]. This review will discuss clinical findings, experimental findings and potentially preventable underlying pathogenetic mechanisms.

Type 2 diabetic encephalopathy

Epidemiology

There are now a number of studies in different ethnic groups demonstrating a linkage between T2DM and mild cognitive impairment (MCI) and AD. Projected increases

in the prevalence of diabetes and dementia show similar and parallel trends (Fig. 1a, b). The coexistence of cerebrovascular disease and T2DM appear to enhance the correlation with MCI and the development of dementia [26–28], underlining the common relationship between T2DM and cerebrovascular disease.

Several studies have demonstrated an increase of AD in T2DM patients compared to non-diabetic individuals. The Rotterdam Study [3] examined over 6,000 patients 55 years and older over a 2-year period using the MMSE and Geriatric Mental State Schedule. In this study, T2DM showed a doubling of the risk for developing dementia. Patients treated with insulin were at an even higher relative risk being 4.3-fold. Arvanitakis et al. [4] examined some 800 nuns and priests longitudinally over 9 years. Fifteen percent of the cohort had or developed T2DM and showed

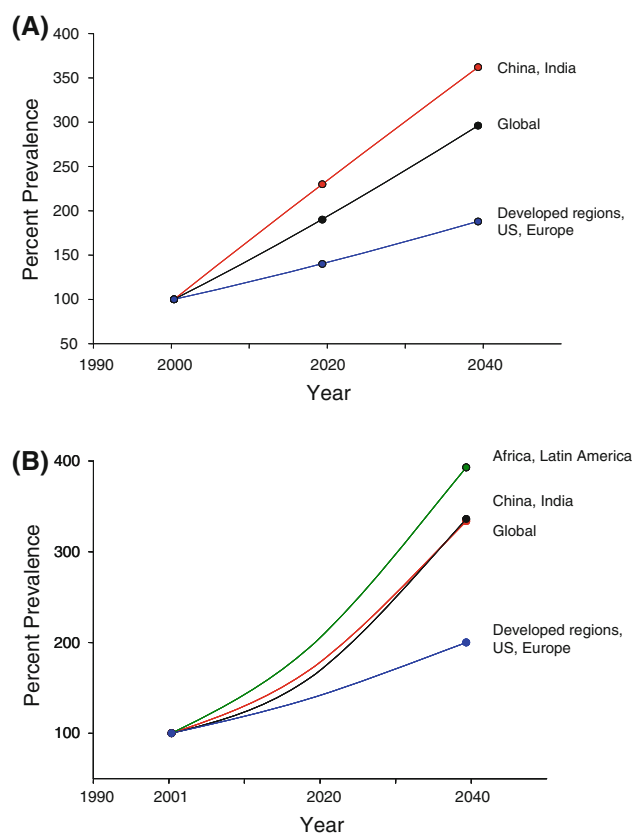


Fig. 1 Projected increases in the prevalence of diabetes (a) and dementia (b) over the next 30 years. The projected increases in diabetes in all age groups are not uniform in various countries. Most rapid increases in diabetes are expected to occur in heavily populated areas of the globe such as India and China. The increases in developed countries, US and Europe will be less (Sources [136, 137]). The predicted prevalence of dementia (b) is similar to that of diabetes, being highest in Latin America, Africa, China and India. The increase in developed countries, US and Europe is anticipated to be less than the global average (Source [138])

a 65% increased risk for developing AD. The Honolulu-Asia Aging Study [28, 29] examining 2,574 Japanese Americans showed a 1.8-fold higher risk for developing AD and 2.3-fold risk for vascular dementia. The risk for developing AD increased significantly to 5.5-fold in those T2DM patients who also had the APOE 4 ϵ allele, compared to patients who had neither T2DM nor the APOE 4 ϵ allele. It should be noted though that the Framington study found an increased risk for AD in patients who were negative for the APOE 4 ϵ genotype [30].

In a follow-up study of the Honolulu-Asia Aging Study [29], in which the authors examined the association between fasting insulin levels and dementia, they found increased risk for dementia in patients with the lowest and highest 15% percentiles of fasting insulin levels. A recent study of patients of ≥ 75 years of age showed that uncontrolled and/or undiagnosed diabetes increased the risk for AD more than twofold [31]. However, negative studies have also been reported showing non-significant relationships between T2DM and AD but with a higher relationship between T2DM and vascular dementia [5, 28]. The hazard ratios of AD in T2DM patients from various studies are summarized in Table 1.

A number of studies have addressed the different components of the metabolic syndrome and cognitive decline. With respect to hypertension, there are generally decreased cognitive performances in hypertensive compared to normotensive individuals [32]. Follow-up studies show increased risk over time and that hypertension during midlife is associated with increased risk of cognitive deficits and dementia at later age [33]. Hypertension causes arterio- and atherosclerotic changes of large cerebral vessels and may severely compromise cerebral perfusion by

luminal narrowing of arterioles resulting in hypoxemia with infarctions and white matter changes (leukoarioses) [34, 35]. Controlled trials employing antihypertensive compounds have provided mixed results. Few studies have reported beneficial effects on dementia [36, 37]. Hence, hypertensive cerebral vasculopathy may further enhance the effects of diabetic microangiopathy with adverse effects on microcirculation. Obesity is associated with poorer cognitive scores and as with hypertension, obesity in midlife leads to worse cognitive performances in late life [33]. Obesity is coupled with leptin metabolism controlling storage and mobilization of fat. Impaired leptin homeostasis increases the amount of extracellular amyloid- β and tau phosphorylation in animal models. Administration of leptin resulted in improvement in cognitive performance, reduction of extracellular amyloid- β and reduction of tau phosphorylation [38]. In AD, reduced circulating levels of leptin are inversely correlated with the severity of cognitive deficits. Hyperlipidemia has in some studies been reported to be associated with increased risk of cognitive deficits [39], whereas others show reversed associations [40]. Pathological and experimental data suggest a pathogenetic role for elevated cholesterol levels in cognitive impairment and dementia (see below).

Imaging studies in type 2 diabetes

Normal aging is associated with an increased incidence of both symptomatic and silent cerebral infarcts [41] and with an increased prevalence of white matter lesions approaching 100% at age 85 [42]. Also with increasing age, there is a global loss of brain volume involving both gray and white matter [43].

Table 1 Hazard ratios (HR) for developing AD in T2DM from various large epidemiological studies (references in brackets)

Study (Ref)	Number of patients	Mean age (years)	Length of follow-up (years)	Patients with diabetes (%)	HR (95% CI)
Leibson et al. [135]	6,775	45–99	14.0	21.5	1.59 (1.25–1.98)
Ott et al. [3]	6,370	>55	2.1	10.9	1.9 (1.2–3.1)
Peila et al. [28]	2,574	72	11.0	35.0	1.8 (1.1–2.9)
					5.5 (2.2–13.7) ^a
Xu et al. [5]	1,301	>75	6	8.8	1.3 (0.9–2.1)
Arvanitakis et al. [4]	824	>55	5.5	15.4	1.65 (1.10–2.47)
Akomolafe et al. [30]	2,210	70	12.7	21.5	1.07 (0.65–1.75)
					4.77 (1.28–17.72) ^b
Xu et al. [134]	1,173	>75	9	4.0	1.77 (1.06–2.97)
					2.52 (1.35–4.70) ^b

Number of patients in each study, mean age, length of follow-up and percent of patients with diabetes in each cohort. Differences in HR between cohorts with Apo 4 ϵ positive patients may reflect relatively small numbers in each study cohort and possibly racial differences between study groups

^a Hazard ratios in patients who were carriers of the Apo 4 ϵ allele

^b Hazard ratios in patients who were non-carriers of Apo 4 ϵ

The incidence of lacunar and silent infarcts increases up to twofold in T2DM patients compared to matched non-diabetic individuals [41, 44]. Recent population-based studies also demonstrate an increased incidence of white matter lesions in patients with type 2 diabetes [44–46]. Type 2 diabetic patients compared to non-diabetic individuals show reduced volumes of hippocampus and amygdala [47, 48] and a threefold increased risk for medial temporal lobe atrophy [49]. Some studies have shown a relationship between white matter lesions, brain atrophy and cognitive function [50, 51]. There is evidence to suggest that these progressive deficits in brain structure may develop already in patients with pre-diabetes [18]. Single components that comprise the metabolic syndrome also impact on brain pathology. Hypertension without diabetes is a known major risk factor for stroke and white matter atrophy [41, 52]. Hyperlipidemia per se is associated with increased risk of stroke [53].

From longitudinal clinical studies, it is therefore clear that the linkages between T2DM, dementia and Alzheimer's disease are multiple. Age alone is an important factor which enhances the vulnerability of the brain to other insults. Of the attributes of diabetes alone, hyperglycemia per se is of pathogenetic impact. Another not always considered factor is the early perturbations of insulin resistance, leading to impaired insulin signaling and hyperinsulinemia with downstream effects on various nerve growth factors, inflammation, tau and amyloid handling [54, 55]. Below an attempt will be made to construct a pathogenetic scheme linking type 2 diabetes to Alzheimer's disease.

Mechanisms underlying Alzheimer's disease in type 2 diabetes

From the epidemiological data referred to above, it is clear that the mechanisms underlying the increased incidence of AD in diabetes and metabolic syndrome are multifold. Undoubtedly, advancing age is a major factor. Hyperglycemia is an important factor in reducing cerebral blood flow by decreasing vasodilatation [56]. Vasodilatation is mainly mediated by NO synthesized in endothelial cells by endothelial NO synthase (eNOS). eNOS expression is reduced in a hyperglycemic environment, probably by reduced protein kinase C (PKC) [57] and increased activity of NADPH-oxidase [58]. Hence, such effects on vasoreactivity will in addition to pathological changes of the microvasculature referred to above compromise cerebral microcirculation.

Insulin-related mechanisms

With increasing age, there is a decrease in cerebral insulin and IGF levels and a desensitization of their respective

receptors with impaired downstream signaling activities. However, the expression of for example the insulin receptor is not necessarily down-regulated, whereas that of the IGF-1 receptor usually is [59–61]. Such age-related changes become more accentuated with AD and are accompanied by increased levels of circulating insulin.

In the brain, insulin and IGF-1 mediate a myriad of effects, such as glucose utilization and energy metabolism, oxidative stress, gene regulation of other neurotrophic factors and their receptors, cholinergic gene expression, expression and phosphorylation of neuroskeletal proteins including tau and regulation of β -amyloid, and they have anti-inflammatory and anti-apoptotic effects [61–64]. Impaired insulin/IGF-1 signaling due to insulin resistance in T2DM impairs tyrosine phosphorylation and phosphorylation of IRS molecules with downstream inhibitory effects on the extracellular signal-related kinase/mitogen-activated protein kinase (ERK/MAPK) pathway, as well as the phosphatidylinositol 3-kinase/phosphorylated Akt (P13 kinase/Akt) pathway and glycogen synthase kinase 3 β (GSK-3 β) (Fig. 2). Impaired insulin-signaling activity acts unfavorably on the expression and translocation of several transcription factors such as nuclear factor kappa light-chain enhancer of activated β -cells (NF κ B) and the cyclic

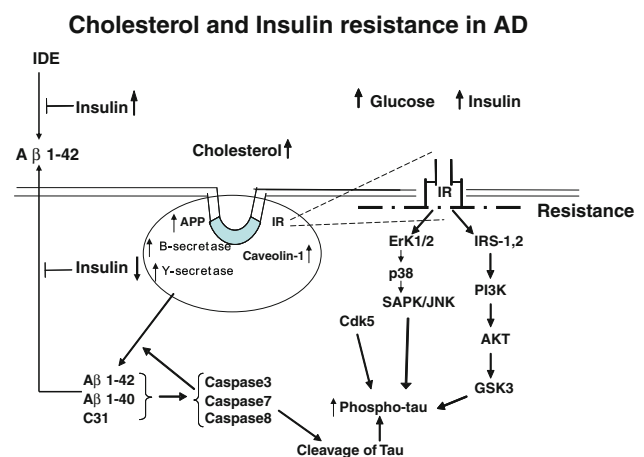


Fig. 2 Relationships between insulin resistance, amyloid metabolism and phospho-tau. The insulin receptor itself appears to be unaffected by T2DM, although insulin resistance affects both the MAP-kinase and P13-kinase pathways with generation of several stress-kinases like GSK-3 β and Cdk5. They induce apoptotic stressors on their own (not indicated). Elevated cholesterol levels induce increased expression of caveolin-1 with downstream increases in APP, β -secretase and γ -secretase with consequent production of A β ₁₋₄₂, A β ₁₋₄₀ and C31 (CTF). These amyloid products induce caspases-3, -7 and -8, which result in cleavage of tau, which is phosphorylated by various kinases most prominently GSK-3 β . Increased levels of insulin consumes IDE, which also degrades A β resulting in increased extracellular A β . Furthermore, inhibition of insulin-signaling causes decreased excretion of A β to the extracellular space with increased intracellular A β

AMP response element-binding protein (CREB) and GSK-3 β with effects on proinflammatory factors and apoptosis [63–65].

Increased expression of NF κ B occurs via phosphorylation of I- κ B, due to impaired insulin signaling, with disinhibition of NF κ B [66, 67]. Activation of NF κ B also occurs in the presence of high glucose. NF κ B plays a central role in the initiation of the inflammatory cascade with the activation of tumor necrosis factor- α (TNF- α), interleukins and C-reactive protein [68–70]. The upregulation of TNF- α has an inhibitory effect of insulin and IGF-1-signaling, thereby providing a self-perpetuating loop [70]. NF κ B is also a modulator of apoptosis and ROS production.

Impaired insulin signaling suppresses early gene responses of c-fos and c-jun with consequences for the expression of IGF-I, IGF-II, NGF and NT-3 expression and their receptors [71, 72]. Both insulin and NGF provide significant neurotrophic support in hippocampus [73, 74]. Insulin is closely tied to neurotransmitter synthesis including acetylcholine and glutamate and NGF exerts a protective effect on cholinergic neurons [74]. Recent advances in our understanding of incretin hormones have led to advances in treating T2DM. Glucagon-like peptide-1 (GLP-1) receptor agonists have shown to be effective in lowering glucose and enhance insulin action [75]. Experimental studies of STZ-diabetic transgenic mice treated with GLP-1 have revealed exciting data showing amelioration of amyloid- β and tau levels [76]. It is therefore almost certain that impaired insulin action plays an important and central role in the increased susceptibility for AD in T2DM.

Amyloid deposition

The hallmarks of AD are the deposition of amyloid-beta ($A\beta$) and the presence of hyperphosphorylated tau isoforms in neurofibrillary tangles. $A\beta$ deposition is associated with impaired insulin signaling, although other mechanisms (see below) are also contributory. Inflammation with activation of microglia promotes $A\beta$ accumulation [77] and amyloid precursor protein (APP) expression and cleavage increase with oxidative stress [78].

Direct effects of insulin on $A\beta$ deposition are twofold. It has been shown both experimentally and in humans that insulin enhances $A\beta$ release from neurons [79]. Furthermore, the insulin-degrading enzyme (IDE) degrades both $A\beta$ and insulin [79] (Fig. 2). Therefore, in a situation of elevated insulin levels, insulin resistance will increase intracellular $A\beta$ and favor extracellular accumulation of $A\beta$ (Fig. 2). The net effect of insulin resistance and hyperinsulinemia is therefore increased levels of intracellular and extracellular $A\beta$, respectively.

The role of cholesterol

There is now both clinical and experimental data supporting the concept that increased cholesterol levels are involved in amyloidogenesis. The amyloidogenic processing of APP occurs in membrane rafts or so-called caveolae of the cell membrane. These are membranous microdomains enriched in cholesterol, sphingolipids and saturated phospholipids [80, 81], and harbor caveolins as well as the insulin and IGF-I receptors. The abnormal processing of APP to $A\beta$ and C-terminal fragment of APP (CTF) occurs in the caveolae and is mediated by β - and γ -secretases (Fig. 2). The normal processing of APP to soluble APP α (sAPP α) occurs outside the domains of the caveolae [81]. There is evidence suggesting that high cholesterol levels increase the number and the size of caveolae and regulates the levels of caveolin-1, with increased expression of APP, activation of β - and γ -secretases and hence the formation of $A\beta$ [82–85] (Fig. 2). A further factor regulating cholesterol homeostasis is the ϵ 4 allele of Apo E, which is identified as an important risk factor in AD [86, 87]. This is not totally unexpected since Apo 4 ϵ is a lipoprotein that carries and facilitates the transport and incorporation of cholesterol within caveolae. Its expression increases the formation of $A\beta$ fibrils and decreases sAPP α yielding a reciprocal regulation of $A\beta$ and sAPP α [88, 89]. Indeed, in vivo experimental studies show that high-cholesterol diets increase $A\beta$ levels and that cholesterol depletion inhibits $A\beta$ generation [90, 91]. It should be mentioned though that brain cholesterol is not solely dependent on dietary uptake or hepatic synthesis but appears to be derived also from in situ synthesis [92]. Evidence suggests that for instance statins not only lower cholesterol levels (both systemic and endogenous) but also suppresses β -secretase activity in caveolae and promotes that of α -secretase, thereby directly attenuating abnormal APP metabolism [81].

Tau processing

Tau plays a major role in regulating microtubules, axonal transport and neuritic outgrowth. Abnormal phosphorylation results in tau dysfunction occurring in multiple neurodegenerative disorders and constitutes the major component of paired helical filaments that make up the neurofibrillary tangles in AD.

The linkage between abnormal APP handling and aberrant phosphorylation of tau is not well understood. Activation of several caspases occur secondary to impaired insulin signaling [54, 93–95] and to amyloidogenic APP metabolism [61, 96] and are believed to initiate proteolytic cleavage of tau (Fig. 2). Once cleaved, tau loses its inhibitory domain of the C-terminal, hence allowing N-terminal fragments to phosphorylate and polymerize [97]. Exposed

epitopes are susceptible to phosphorylation by various kinases, some of which emanate from the compromised insulin-signaling cascade such as GSK-3 β , PP2A and Cdk5 [61] (Fig. 2). Such mechanisms possibly link the amyloidogenic APP metabolism as well as impaired insulin signaling to abnormal tau disposition in AD.

Potential therapeutic approaches

As alluded to above, several approaches to alleviate the progression of AD in T2DM have been explored, such as lipid-lowering compounds, anti-hypertensive and insulin enhancing medications such as GLP-1 receptor agonists. Another compound that has undergone clinical trials is acetyl-L-carnitine (ALC) supplementation. It enhances acetylcholine production based on oxidative metabolism and elevation of ATP, improves oxidative stress, inhibits hippocampal excitotoxicity and enhances responses to NGF. ALC has demonstrated beneficial effects on several peripheral neuropathies including diabetic neuropathy. Given to patients with AD, ALC has demonstrated improvements in behavioral deficits such as short- and long-term memory, spatial learning tasks and tasks of personal recognition [98, 99].

Animal studies

Several studies using transgenic or knockout models with streptozotocin-induced diabetes have linked insulin and IGF-1 signaling to abnormal tau and APP handling. Relatively few studies, though, have utilized genetically non-manipulated type 2 diabetic animal models to study the relationship with AD.

We have reported on the spontaneously type 2 diabetic BBZDR/Wor rat, which develops obesity, hyperglycemia, insulin resistance with hyperinsulinemia as well as elevated cholesterol levels, hence closely mimicking the human disorder [61, 100]. After 8 mo of diabetes, this model exhibits severe neuronal loss in frontal cortex associated with significant decrease in presynaptic densities, profound gliosis and a ninefold increase in degenerating neurites compared to age-matched control rats [61, 100]. In the same model, the insulin receptor is not downregulated, whereas insulin-signaling intermediaries are suppressed signifying insulin resistance. However, the expression of the IGF-IR itself is downregulated in frontal cortex (Fig. 3). These abnormalities were accompanied by marked increases in APP, β -secretase, A β and CTF (Fig. 4), as well as a 2.5-fold increase in hyperphosphorylated tau. The amyloidogenic APP metabolism was associated with a significant increase in caveolin-1 expression (Fig. 4). The latter is probably linked to hypercholesterolemia in this model [61]. This was confirmed by in vitro studies and was

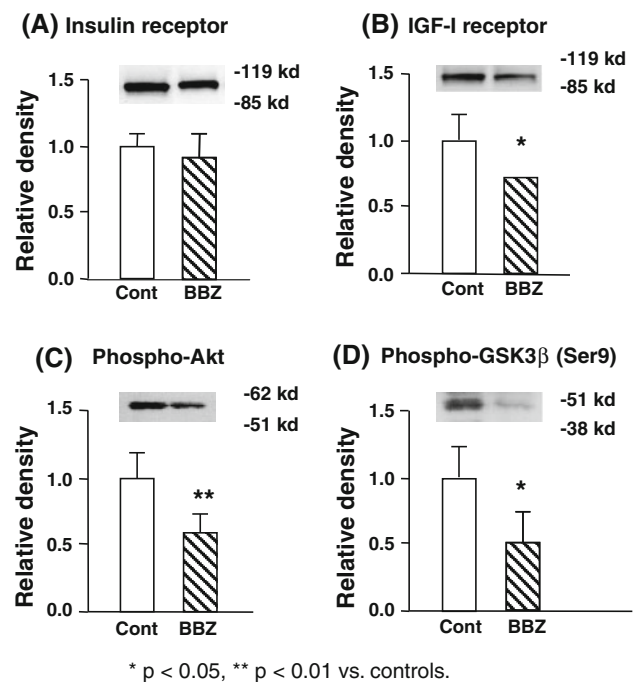


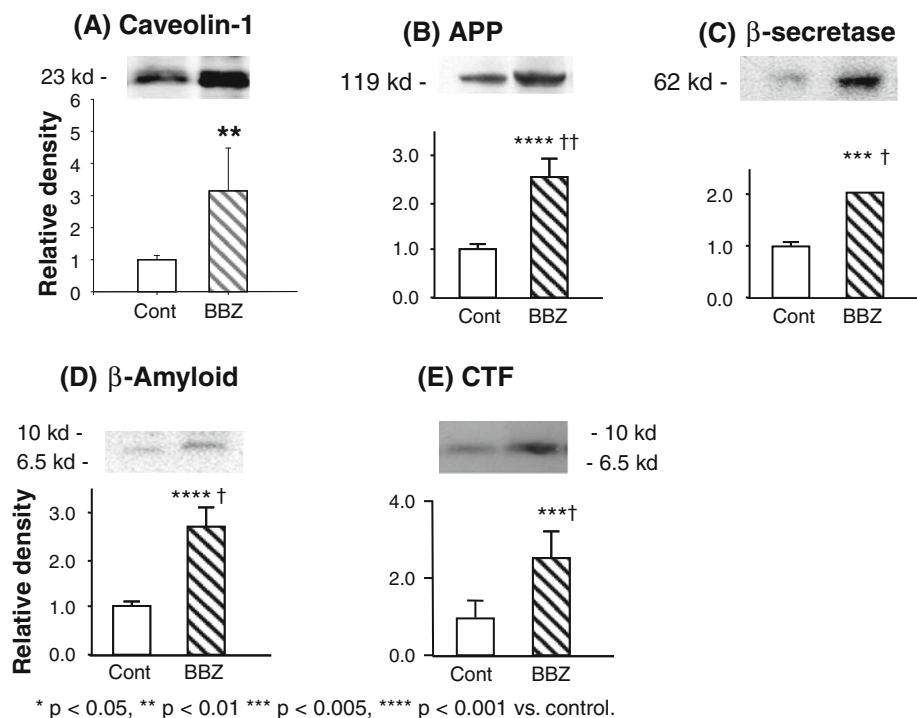
Fig. 3 In the type 2 diabetic BBZDR/Wor rat, the expression of the insulin receptor is not affected in the frontal cortex (a) after 8 months of diabetes, whereas the IGF-I receptor (b) is significantly ($P < 0.05$) downregulated. Insulin-signaling intermediaries such as p-Akt (c) and GSK-3 β (Ser 9) (d) are downregulated indicating resistance of the insulin signaling (cf. Fig. 2). (Data compiled from [61])

further accentuated by exposure to Apo4E [85]. Similar but substantially milder changes were observed in the type 1 counterpart model, the BB/Wor rat [61, 100], which is consistent with recent findings in the type 2 db/db mouse model and in a type 1 STZ mouse model [101]. Therefore, in these models central insulin-resistance and increased exposure to cholesterol can be directly linked to amyloidogenic APP handling and hyperphosphorylation of tau, the very hallmarks of AD.

Summary T2DM encephalopathy

Based on these clinical and experimental data, there are undoubtedly mechanistic connections between T2DM and AD perpetuating the latter in T2DM patients. It appears that insulin resistance plays a central role with direct effects on amyloid and tau accumulations and indirect effects via apoptotic and oxidative stressors. Furthermore, impaired insulin action affects other neurotrophic factors, neurotransmitters and structural neuroskeletal proteins leading to neurite degeneration. Other common clinical abnormalities associated with T2DM, such as hyperlipidemia and obesity, appear to accentuate the abnormalities caused by insulin resistance, such as enhanced amyloidogenic processing of APP and activation of innate inflammatory factors with further adverse effects on insulin

Fig. 4 In 8-month diabetic BBZDR/Wor rats caveolin-1 (a), amyloid precursor protein (APP) (b), β -secretase (c) and β -amyloid (d) and CTF (e) are upregulated, in part as a consequence of elevated cholesterol levels. Increased activities of caspases, consequent to amyloid production and impaired insulin signaling, result in splicing of tau with increased accumulation of intracellular phospho-tau. (data partly extracted from [61])



signaling, oxidative and apoptotic stressors eventually resulting in neuronal loss.

Although many questions remain as to the detailed linkages between the two disorders, certain relationships are becoming increasingly clear. Therefore, continued investigations are needed in order to start to formulate potential therapeutic interventions in order to curtail the increase of these two major epidemics and their relationship.

Type 1 diabetic encephalopathy

Epidemiology

In the last decade, it has become increasingly evident that type 1 diabetes has adverse effects on CNS function and cognition. Neurobehavioral studies in children with T1DM have demonstrated shortcomings in attention, processing speed, executive function, intelligence and memory. These deficits result in lower IQ performances and greater likelihood for poor school performances [20, 102–104]. One study showed that early onset of diabetes was associated with lower IQ performances and lower full-scale IQ [104]. It has been recognized that early onset of T1DM results in worse neuropsychological performances [20, 102, 105] and that males are more vulnerable than females [20, 106]. In contrast to earlier beliefs, most studies have not associated cognitive deficits with repeated episodes of hypoglycemia due to intensive insulin treatment [22, 23, 107]. It is

evident that the incidence of T1DM is increasing globally, and this increase is greatest in younger age groups [108–111]. These epidemiological data are concerning, since the metabolic insult of T1DM will affect children in whom the still developing brain is more susceptible [21].

Imaging studies in T1DM

Studies of patients with onset before the age of six have demonstrated a high incidence of mesial temporal lobe sclerosis, which could not be associated with previous episodes of hypoglycemia [112]. Volumetric MRI studies in patients with diabetes for 12 years showed significant decreases in white matter volumes in parahippocampus, temporal and frontal lobes as well as decreased gray matter volumes of the thalami, hippocampi and insular cortex [104]. Voxel-based morphometric analyses of patients with T1DM for 15–25 years duration showed decreased gray matter densities in thalami, superior and middle temporal gyri and frontal gyri [113]. It therefore appears that limbic temporal and frontal structures are most vulnerable. Only few recent neuropathological reports describe structural abnormalities. Two young diabetic patients with diabetes since age four and who succumbed to ketoacidosis showed marked neuronal loss in hippocampus and frontal cortex and white matter atrophy of frontal and temporal regions [114]. These findings were associated with marked down-regulation of both insulin and IGF-I receptors and activation of pro-inflammatory factors. Such structural deficits probably underlie cognitive deficits such as memory,

information processing, executive function and attention and have been related to impaired functional connectivity [115] and loss of fast β -frequency bands on quantitative EEG [25]. It is therefore now becoming accepted that T1DM results in various cognitive deficits related to gray matter deficits, particularly in limbic structures as well as white matter atrophy. Such deficits are more prevalent in patients with onset of diabetes at a young age.

The reason for the recent increase in the incidence of T1DM not only in Europe [111] but also in rapidly developing countries such as the Asian countries [110] is not known. Several possibilities have been put forward pertaining to changing environmental factors such as increased incidences of Cesarean sections, formula feeding rather than breast feeding, decreased exposure to childhood infections as well as obesity and inflammation. It has been postulated that the rising prevalence of childhood obesity with associated inflammation could lead to accelerated autoimmunity targeting pancreatic β -cells [116]. Childhood obesity even in the very young is anticipated to show a multifold increase in heavily populated countries like China and India [117, 118]. Hence, the disproportionate increase in T1DM in the very young children taken together with projected increases in large population areas of the globe is indeed worrisome as to the likely cognitive consequences.

Mechanisms underlying cognitive dysfunction in type 1 diabetes and animal studies

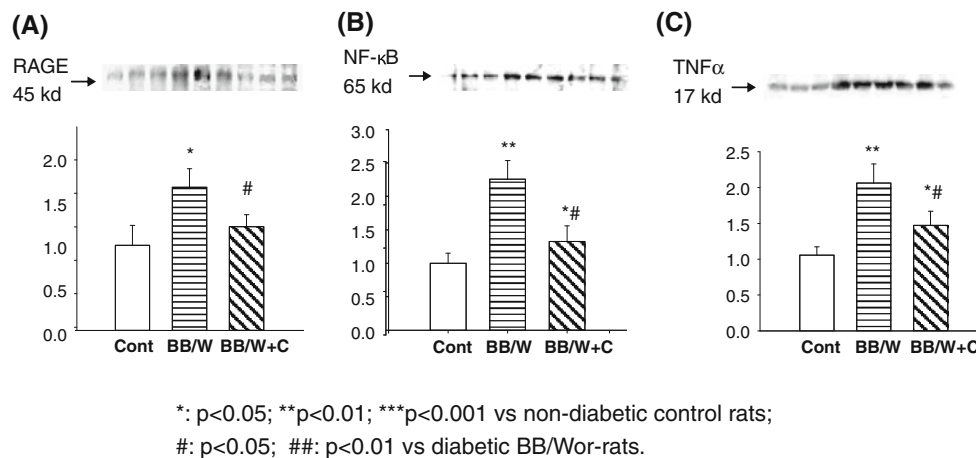
From the epidemiological data referred to above, it is clear that age is of importance with greater adverse impacts on the developing brain. Only few studies in patients have addressed potential underlying factors. One single-photon emission tomography study showed impaired cerebral blood flow in frontal areas and basal ganglia [119]. Chronic hyperglycemia has been associated with impaired performances on neuropsychological tests [20, 103] and structural changes [120]. Structural abnormalities have been accompanied by increased sorbitol and decreased taurine levels, suggesting activation of the polyol-pathway and impaired neurotrophic support [121]. Recently, we demonstrated postmortem decreased expression of the insulin and IGF-I expression in hippocampus, cerebellum, pons and basal ganglia in two patients with early onset of diabetes, changes which were associated with severe neuronal loss in hippocampus and frontal cortex [114].

On the other hand, systematic studies in type 1 diabetic animal models are starting to emerge. Studies in streptozotocin-induced (STZ) diabetes in rats have demonstrated neurobehavioral deficits using the Morris water maze technique, associated with impaired hippocampal long-term potentiation [122]. This measure being reflective of

synaptic plasticity in hippocampus was prevented by insulin treatment, whereas interventional insulin treatment to normalize hyperglycemia had only a partial effect on long-term potentiation [123].

Changes in cerebral somato-sensory, visual and auditory evoked potentials occur in the STZ- and spontaneously diabetic BB/Wor rat. Such changes are followed by degenerative changes in the dorsal columns of the spinal cord and the optic nerve and are modified by insulin treatment [1, 124–126]. The BB/Wor rat model shows complete insulin- and C-peptide deficiencies and severe hyperglycemia and is maintained by small daily insulin doses [24, 95]. Longitudinal studies in this model have revealed early neurobehavioral abnormalities using the radial arm maze occurring after 3 months of diabetes and were associated with marked down-regulation of the IR, IGF-IR, IGF-I and IGF-II as well as NGF and NGF-R-TrA expression in hippocampus [24, 54, 95]. These early neurobehavioral deficits have been related to long-term potentiation and early pathology of hippocampal mossy fibers [24, 127, 128]. Diabetic rats given full replacement of insulinomimetic C-peptide from onset of diabetes showed full prevention of the early neurobehavioral deficits and significant prevention of neurotrophic factors expression in hippocampus [24, 95]. C-peptide replacement does not effect hyperglycemia. Instead, the glucose metabolic rate was increased approximately threefold in various brain regions in diabetic rats [24]. The findings were associated with severe compromise of the insulin signaling as measured by decreased levels of p-Akt and GSK-3 β [24, 95]. These data suggest that insulin deficiency and impaired signaling may have a greater impact on the early abnormalities than does hyperglycemia.

Both insulin and NGF provide important functions in hippocampus with respect to acetylcholine and glutamate synthesis and protection of cholinergic neurons [73, 74, 129]. In 4-month diabetic rats, this was reflected in a severe suppression of presynaptic synaptophysin and a marked decrease in presynaptic densities. Interestingly, these deficits were fully prevented by C-peptide substitution [24]. Only at 6 months were late cognitive functional deficits evident, using the Morris water maze paradigm, reflecting problem solving, storage and retrieval of relevant information and long-term memory [65]. Such changes were associated with marked upregulation of post-synaptic excitatory Glu R2, which has been associated with long-term suppression and memory formation [24]. The cognitive deficits increased over time and were almost fully prevented by C-peptide replacement from onset of diabetes [24, 95]. C-peptide is part of the proinsulin molecule and splits off from and is secreted in equimolar concentrations with insulin. It binds to a variety of cell types with stimulation of multiple signaling pathways including



*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$ vs non-diabetic control rats;
#: $p < 0.05$; ##: $p < 0.01$ vs diabetic BB/Wor-rats.

Fig. 5 Activation of innate inflammatory responses in hippocampus of 7-month type 1 diabetic BB/Wor rats and those replenished with C-peptide from onset of diabetes. NF κ B (a), RAGE (b) and TNF- α

(c) expression showed upregulations in diabetic rats, which was significantly prevented by C-peptide. (data extracted from [70])

enhancement of insulin signaling [130]. Experimental data points strongly to the existence of a G-protein-coupled receptor, although this has not been identified. A recent comprehensive update on C-peptide biology is reviewed in reference [131].

Similar data have been reported in STZ-induced Swiss-Webster mouse, which shows down-regulation of insulin-signaling intermediaries, transcription factors like cAMP and CREB and synaptophysin [64, 132]. Some of these transcription factors are involved in the gene regulation of neurotrophic factors [24]. Interestingly rather than C-peptide, intranasal insulin administration slowed the neurobehavioral deficits and corrected the impaired insulin signaling [64]. In the STZ-Swiss Webster mouse, the authors described upregulation of the receptor for advanced glycation end products (RAGE) which was associated with white matter atrophy [112]. Similarly, the BB/W rat shows upregulation of NF κ B and RAGE associated with activation of TNF- α and proinflammatory interleukins, whereas the anti-inflammatory IL-10 was significantly suppressed (Figs. 5, 6) [24, 70]. Somewhat surprisingly, both NF κ B, RAGE and downstream pro- and anti-inflammatory factors were corrected following C-peptide replacement [24, 70]. These findings suggest that the activation of the inflammatory cascade is initiated by NF κ B [24, 69, 95], rather than by increased advanced glycosylation end products (AGEs) secondary to hyperglycemia and an activated polyol pathway, since C-peptide does not modify systemic hyperglycemia. It should be noted though that increased NF κ B expression occurs consequent to impaired insulin signaling via phosphorylation of I- κ B [63, 71, 130]. Available animal data therefore suggest that early cognitive deficits in type 1 diabetes occurs mainly due to insulin and C-peptide deficiencies and their impaired signaling, rather than due to hyperglycemia per se. This is strongly

supported by the data demonstrating prevention of cognitive deficits by administration of systemic insulinomimetic C-peptide or by direct delivery of insulin to the CNS through the intranasal route. These findings when translated to the human situation open up tremendous and easily achievable potentials for preventative and therapeutic avenues for combating type 1 cognitive deficits.

Structural changes in animal models

Toth et al. [64, 112] reported white matter atrophy associated with upregulation of RAGE in the white matter of the STZ-induced diabetic Swiss Webster mouse. Intranasal insulin administration ameliorated white matter atrophy in this model. However, neuronal loss was not evident in this mouse model. In the BB/Wor rat, white matter changes occur early with suppressed expression of the oligomarkers CAII and myelin basic protein [24], loss of white matter oligodendroglial cells, and an associated increase in white matter astrogliosis (Fig. 7). These changes are accompanied by increased expression of RAGE, TNF- α and IL-6 in the white matter and are probably the result of apoptotic oligodendroglial cell death as suggested by increased expression of Bax, cleaved-PARP and activated caspase 3. These white matter changes were substantially prevented by C-peptide replacement [24].

In the BB/Wor rat, insulin and C-peptide deficiencies are associated with oxidative and apoptotic stress [65, 71, 95]. Activation of these stressors was accompanied by increased TUNEL-stain of hippocampal pyramidal cells, increased DNA laddering and neuronal loss of hippocampal pyramidal cell being most profound in the CA1 region [24, 127]. Such changes were preceded by upregulation of post-synaptic excitatory GluR2 subunit, which has been associated with long-term suppression and long-term

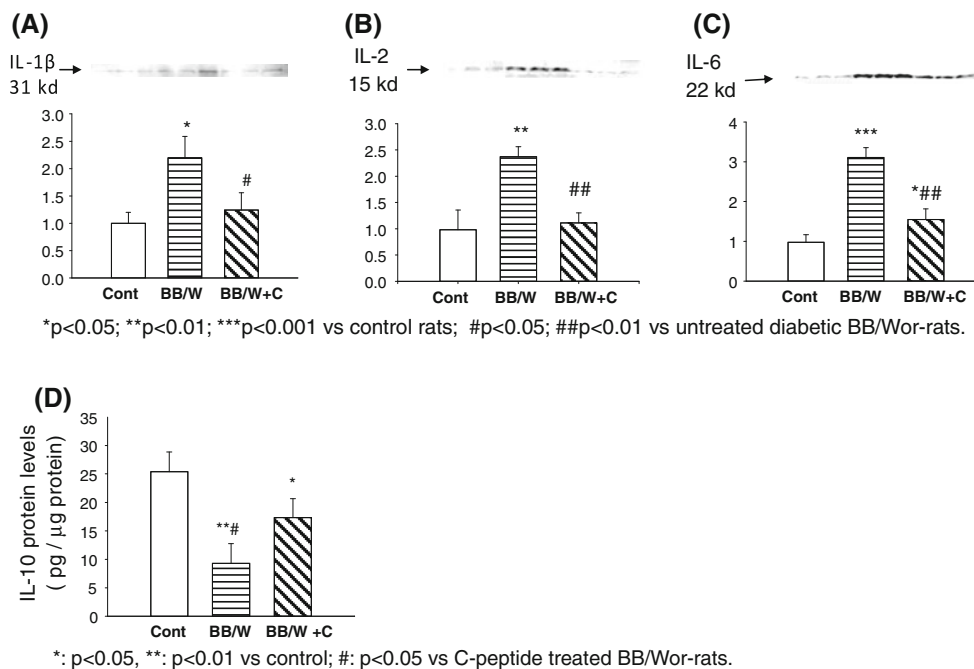


Fig. 6 Simultaneously with the upregulation of NF κ B and TNF α (see Fig. 5) pro-inflammatory IL-1 β (a), IL-2 (b) and IL-6 (c) were upregulated, whereas anti-inflammatory IL-10 (d) was downregulated

in non-treated diabetic rats. C-peptide replacement corrected significantly these abnormalities. (partly reproduced with permission from [70])

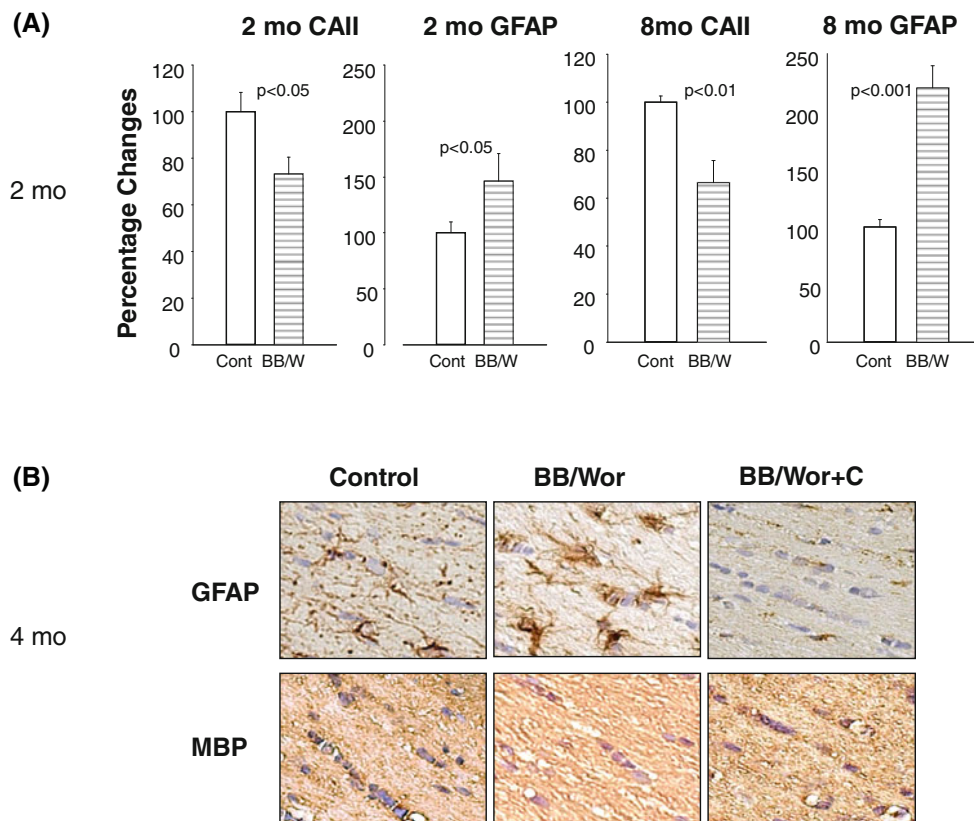


Fig. 7 Expression of the oligodendroglia cell marker CAII and astroglial marker GFAP in the temporal white matter of 2- and 8-month diabetic BB/Wor rat showing decreased expression of CAII and increased expression of GFAP. The immunohistochemical

identification of increased GFAP-positive astrocytes and decreased myelin basic protein (MBP)-labeled oligodendroglia cells in the temporal white matter of 4-month diabetic BB/Wor rats. (reproduced with permission from [24])

memory deficits [24]. As in the earlier occurring changes in the white matter, these sequential abnormalities were significantly prevented by C-peptide replacement with partial but significant prevention of the late cognitive abnormalities [24, 95].

The discrepancies in the development of structural changes in the gray and white matter in the mouse and the rat models are likely to be related to the time of the growth spurts of the gray versus the white matter and the timing of onset of diabetes. In both species as in humans, the gray matter growth spurt precedes that of the white matter [21, 133]. The differences of the growth spurts may therefore explain the earlier changes in the white matter compared to those of the gray matter structures in the rat model. At the time of diabetes onset, the rat model still experiences the white matter growth spurt. Such considerations again underline the enhanced vulnerability in children with early onset of diabetes at a time when the brain is still developing [21, 133].

Summary of T1DM encephalopathy

As imagined, the mechanisms underlying type 1 diabetic encephalopathy are complex and far from fully understood. However, as exemplified by the findings in the animal models of T1DM, certain trends start to emerge. These

suggest that insulin deficiency and its ramifications as to other neurotrophic factors probably play an early and prominent role with effects on transmitters, neurite integrity and connectivity. Associated oxidative stress and activation of apoptotic pathways may be contributed to by hyperglycemia but are probably still mainly the result of impaired insulin signaling as suggested by the correction with C-peptide and intranasal insulin administration, neither of which alters systemic hyperglycemia. Such perturbations will certainly over time lead to neuronal loss and disintegration of neuronal networking fundamental to cognitive function (Fig. 8). It should be mentioned though that the cognitive deficits in T1DM appear to be different than that of T2DM. T1DM is not clinically associated with AD, although as mentioned earlier, mild AD changes may occur also in the type 1 situation.

Despite the dismal epidemiological outlook and predictions of T1DM encephalopathy, the good news is that there are potential glimmers of hope, when considering the encouraging results from interventions in animal studies. It is therefore imperative that we start to explore these logical, relatively simple and inexpensive measures in clinical trials.

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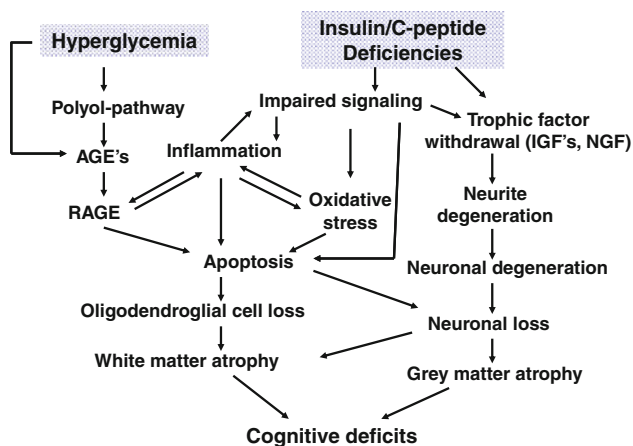


Fig. 8 Proposed sequential mechanisms underlying T1DM encephalopathy based on data from the BB/Wor rat. Insulin and C-peptide deficiencies result in impaired insulin signaling affecting inflammation, oxidative stress and apoptosis. It leads to suppressed expression of neurotrophic factors and their receptors impacting on neuronal integrity with neurite degeneration as well as increased apoptotic activity with neuronal loss and gray matter atrophy. Apoptotic cell loss of white matter oligodendroglial cells results in white matter atrophy. Hyperglycemia and activation of the polyol pathway lead to increased AGE's formation that contributes to increased RAGE expression, inflammation and apoptosis. The progressive deficits in gray and white matter structures of vulnerable areas result in cognitive deficits

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