

**Original Paper**

# Cardiorenal Metabolic Syndrome and Diabetic Cognopathy

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Diabetic cognopathy · Alzheimer's disease · Type 2 diabetes mellitus · Ultrastructure · Remodeling · Neurovascular unit · Blood-brain barrier

**Abstract**

The prevalence of the cardiorenal metabolic syndrome (CRS) is increasing in parallel with obesity, type 2 diabetes mellitus, Alzheimer's disease, and other forms of dementia. Along with metabolic, inflammatory, and immunological abnormalities, there is maladaptive structural remodeling of the heart, kidney, and brain. The term 'diabetic cognopathy' (DC) may be used when discussing functional and structural changes in the brain of the diabetic patient. DC likely represents an advanced form of these changes in the brain that evolve with increasing duration of the CRS and subsequent clinical diabetes. We posit that DC develops due to a convergence of aging, genetic and lifestyle abnormalities (overnutrition and lack of exercise), which result in multiple injurious metabolic and immunologic toxicities such as dysfunctional immune responses, oxidative stress, inflammation, insulin resistance, and dysglycemia (systemically and in the brain). These converging abnormalities may lead to endothelial blood-brain barrier tight junction/adherens junction (TJ/AJ) complex remodeling and microglia activation, which may result in neurodegeneration, impaired cognition, and dementia. Herein, we describe the brain ultrastructural changes evolving from a normal state to maladaptive remodeling in rodent models of CRS including microglia activation/polarization and attenuation and/or loss of the TJ/AJ complexes, pericytes and astrocytes of the neurovascular unit. Further, we discuss the potential relationship between these structural changes and the development of DC, potential therapeutic strategies, and future directions.

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The real voyage of discovery consists not in seeking new landscapes,  
but in having new eyes.  
*In Search of Lost Time* by Marcel Proust (1871–1922)

## Introduction

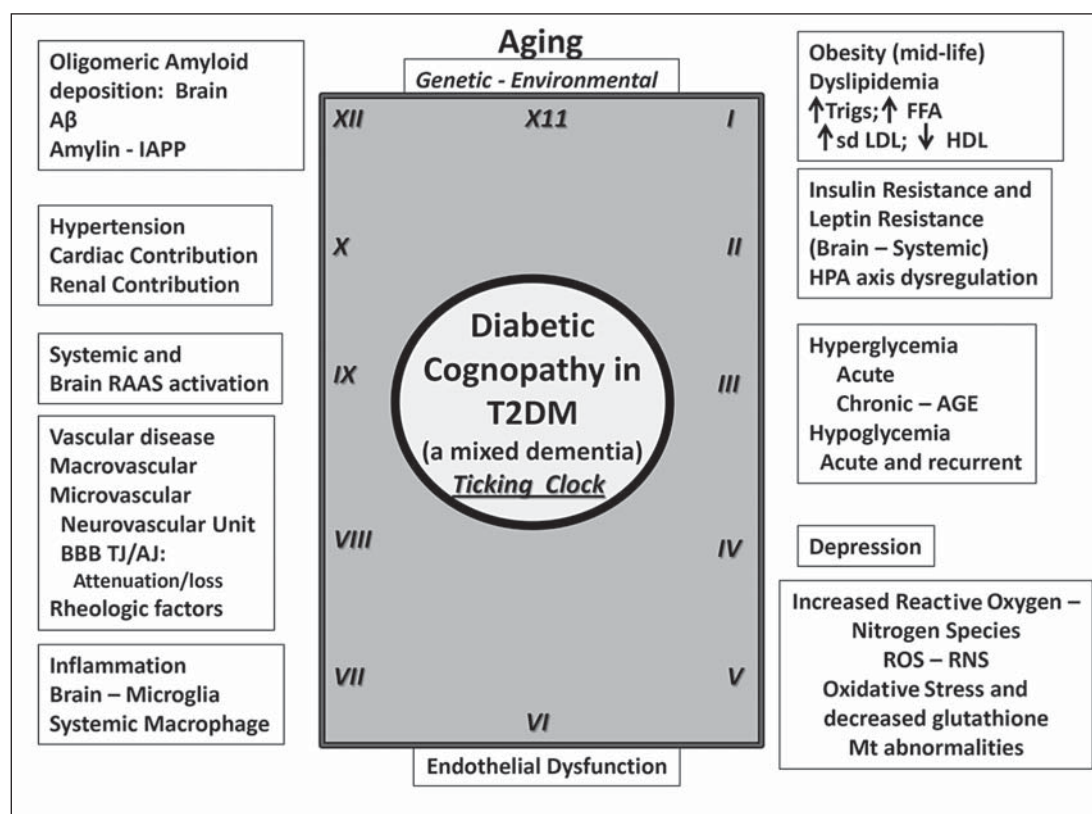
The presence of a group of interactive maladaptive factors, which includes obesity, insulin resistance (IR), hypertension, and altered cardiac and renal function, constitutes the cardiorenal metabolic syndrome (CRS) [1]. The CRS is associated with early cardiac (i.e. diastolic dysfunction), vascular, and renal (i.e. microalbuminuria) disease. Of contemporary interest is the fact that brain maladaptive changes are associated with cognitive impairment and dysfunction (CID) in the CRS, which may lead to diabetes-related CID or diabetic cognopathy (DC) [2]. CRS, type 2 diabetes mellitus (T2DM), cardiovascular disease, chronic kidney disease, and associated DC are also increasing in our overweight and aging population. T2DM and Alzheimer's disease (AD) are strongly associated with IR and amyloid [human islet amyloid polypeptide in pancreatic islets and amyloid  $\beta$  ( $A\beta$ ) in brains] deposition [3]. These conformational disease states share the common abnormality of increased oxidative stress, endothelial dysfunction, and adaptive and innate immunological activation/inflammation [4–10].

T2DM is associated with a 1.5- to 2-fold increased risk of developing dementia [6] and up to a 1.5-fold increase in AD [6–10]. Interestingly, patients who have AD also have an increased risk of developing T2DM [10]. This review will focus on the pathophysiology, functional, and structural remodeling abnormalities in the brain that occur with the CRS and associated DC.

## Cognitive Dysfunction in Diabetes

Cognitive dysfunction in type 1 diabetes mellitus is associated with impaired processing, psychomotor efficiency, attention, and visual construction. The net result is some combination of impaired learning, problem solving, motor speed, vocabulary, general intelligence, visual perception, somatosensory abnormalities, motor strength, mental flexibility, and executive function [2]. The Diabetes Control and Complications Trial, which encompassed an 18-year follow-up of 1,144 patients with type 1 diabetes mellitus, demonstrated moderate declines in motor speed and psychomotor efficiency, without evidence of substantial long-term decline in cognitive function [9]. Additionally, individuals with hemoglobin  $A_{1c}$  <7.4% performed better on tests of motor speed and psychomotor efficiency than those whose hemoglobin  $A_{1c}$  was >8.8%. Together, these observations suggest that sustained hyperglycemia is an important contributor to DC.

T2DM is associated with cognitive abnormalities in three predominant domains of memory (verbal, visual, working, and immediate recall), psychomotor speed, and frontal lobe executive function [2], with altered processing speed, complex motor function, verbal fluency, and attention. Patients with T2DM have a 2-fold increased likelihood of depression, which may negatively affect cognitive function and activities of daily living [7]. In addition to the above cognitive impairments, T2DM patients have an increased risk of vascular dementia (VaD) and up to a 1.5-fold increased risk of developing AD [2, 5, 8, 10, 11]. Recurrent hypoglycemia in T2DM is also associated with a significantly increased risk of dementia [11]. In summary, individuals who evolve from the CRS to T2DM have a greater rate of progression of cognitive decline and a greater risk of developing severe cognitive dysfunction and DC [8]. Over time, this structural remodeling, which starts in the early stages of the CRS, may progress to DC as the metabolic and cardiovascular disease abnormalities of overt diabetes evolve.



**Fig. 1.** Potential causes of DC in CRS. Patients with midlife obesity, CRS or T2DM are a ticking clock for the development of DC due to multifactorial predisposing factors (I–XII). Trigs = Triglycerides; FFA = free fatty acids; HDL = high-density lipoprotein cholesterol; sd LDL = small dense low-density lipoprotein cholesterol; HPA = hypothalamic pituitary adrenal; AGE = advanced glycation end products; RNS = reactive nitrogen species; Mt = mitochondria; BBB = blood-brain barrier; TJ/AJ = tight junction/adherens junction; RAAS = renin-angiotensin-aldosterone system; Aβ = amyloid β; IAPP = islet amyloid polypeptide.

### CRS and T2DM: Relationship to DC

The various metabolic abnormalities associated with the CRS contribute to DC through an increased state of systemic generation of reactive oxygen species (ROS) and reactive nitrogen species and heightened inflammation, which may interact and result in maladaptive brain remodeling/functioning. Excess visceral adiposity is an integral component of the CRS, and is a major contributor to IR, atherogenic dyslipidemia, hyperuricemia, hypertension, albuminuria, and endothelial dysfunction [1]. Visceral adiposity is associated with increased lipolysis, increased circulating free fatty acids, ceramides and other toxic lipid moieties, oxidative stress, and chronic local and systemic inflammation (including macrophage polarization), which results in skeletal muscle, fat, and liver IR. Systemic IR obligates increased insulin secretion by islet β-cells, followed by systemic hyperinsulinemia and hyperamylinemia [12]. The potential causes of DC in the CRS are multifactorial and are summarized in figure 1.

#### *IR, Hyperinsulinemia, and Hyperamylinemia in the CRS*

IR and cognitive dysfunction share common risk factors such as CRS-T2DM, visceral obesity, dyslipidemia, oxidative stress, dysfunctional innate and adaptive immunity, and low-

**Table 1.** Comparison of VaD, AD, MD, and DC

Comparators	VaD	AD	MD	DC
Onset	Abrupt-acute onset with stepwise cognitive decline	Gradual progressive cognitive decline	Both stepwise and gradual progressive	Both stepwise and gradual progressive
Verbal learning and memory	Less impairment	Greater impairment	Variable	Variable
Episodic memory	Less impairment	Greater impairment	Variable	Variable
Executive/attention abilities	Greater impairment	Less impairment	Variable	Variable
Semantic memory, visuospatial perception	Greater impairment	Less impairment	Variable	Variable
Antegrade episodic memory	Less impairment (more problems in information retrieval)	Greater impairment (in encoding new information – long-term memory)	Variable	Variable
ApoE ε4	+/-	Increased risk	Variable	Variable
Anatomical involvement	Variable: depending on the location of vascular obstruction Hypoxia/ischemia Stroke and bleeds	Hippocampal Frontal cortex Parietal cortex Cerebellum	Variable	Variable
Hippocampal atrophy	Less involvement (especially early on)	Greater	Variable	Variable
Motor loss	Greater Acute onset	Gradual chronic – late in disease	Variable	Variable
White matter intensities – lesions on MRI	Greater	Less	Variable	Variable
Vascular involvement	Greater Macrovascular Microvascular Disease	Microvessel: less or absent	Variable	Variable
BBB dysfunction: TJ/AJ dysfunction, attenuation, and/or loss – appears early in most dementias and is one of the focuses of this review	Positive	Positive	Positive	Positive
Aβ plaques Senile plaques Neurofibrillary tangles	Negative; however, may be found at autopsy	Positive Gold standard	Variable	Variable
Depression	Greater	Less	Variable	Greater/ variable
General memory	Less severe; however, VaD catches up with AD at the level of moderate impairment	More severe memory loss Develops early on	Variable	Variable
Endothelial dysfunction, oxidative stress	Early involvement	Similar	Similar	Similar
Risk factors multiple	Similar	Similar	Similar	Similar

The greatest differences are to be found when comparing VaD and AD. Note that MD and DC are similar since DC may be thought of as an MD. The rigid lines and distinctions that have been drawn in the past between VaD and AD have become less rigid. Currently, these rigid distinctions may no longer be tenable since the two disorders share common clinical features, risk factors, neuropathology, and hemodynamic changes. Note that the risk factors are similar in VaD, AD, MD, and DC. Shared risk factors include advanced age, ApoE ε4 allele, CRS, hypertension, midlife obesity, impaired glucose tolerance, T2DM, hyperlipidemia, cardiovascular disease, atrial fibrillation, smoking, level of education, previous traumatic brain injury, decreased social interaction, decreased mental and physical activity late in life.

grade inflammation [1]. It is thus likely that IR is at the core of DC, VaD, mixed dementia (MD), and AD (table 1). Insulin contributes to normal brain neuronal signaling, plasticity, and repair and trophic effects. Insulin receptors are highly expressed in specific areas of the brain including the olfactory bulb, hypothalamus, cerebral cortex, cerebellum, striatum, and hippocampus, which allow signal transduction of insulin [2, 10, 13]. Systemic IR and chronic hyperinsulinemia result in the downregulation of insulin receptors at the blood-brain barrier (BBB)

[13], thereby impeding insulin transport to the brain, which can result in decreased functional insulin signaling in endothelial cells (ECs), glial cells, and neurons [2, 10, 13].

Amylin may also contribute to the development of DC [14, 15]. Hyperamylinemia correlates with hyperinsulinemia in the CRS and T2DM, and the oligomeric-amyloidogenic human islet amyloid polypeptide has recently been found in the brains of AD patients [16]. It is possible that amylin-derived deposits may act as a nidus for later A $\beta$  deposition in the brain interstitium and perivascular regions, thereby contributing to A $\beta$  senile plaques and cerebral amyloid angiopathy [16]. Leptin is an adipokine produced in adipose tissue which plays an important role in energy homeostasis. Central nervous system (CNS) effects of leptin include modulation of energy homeostasis, feeding behavior, and reproductive function. Central obesity and IR are associated with hyperleptinemia coupled with leptin resistance (LR) and reduced leptin transport across the BBB and into the hypothalamus and hippocampus [15, 17, 18]. The inverse correlation of fasting leptin with gray matter volume in brains from obese individuals as compared to lean individuals suggests an important trophic function. Importantly, impaired leptin transport across the BBB due to hypertriglyceridemia coupled with peripheral LR and hypothalamic LR may play an important role in the development and progression of obesity [18].

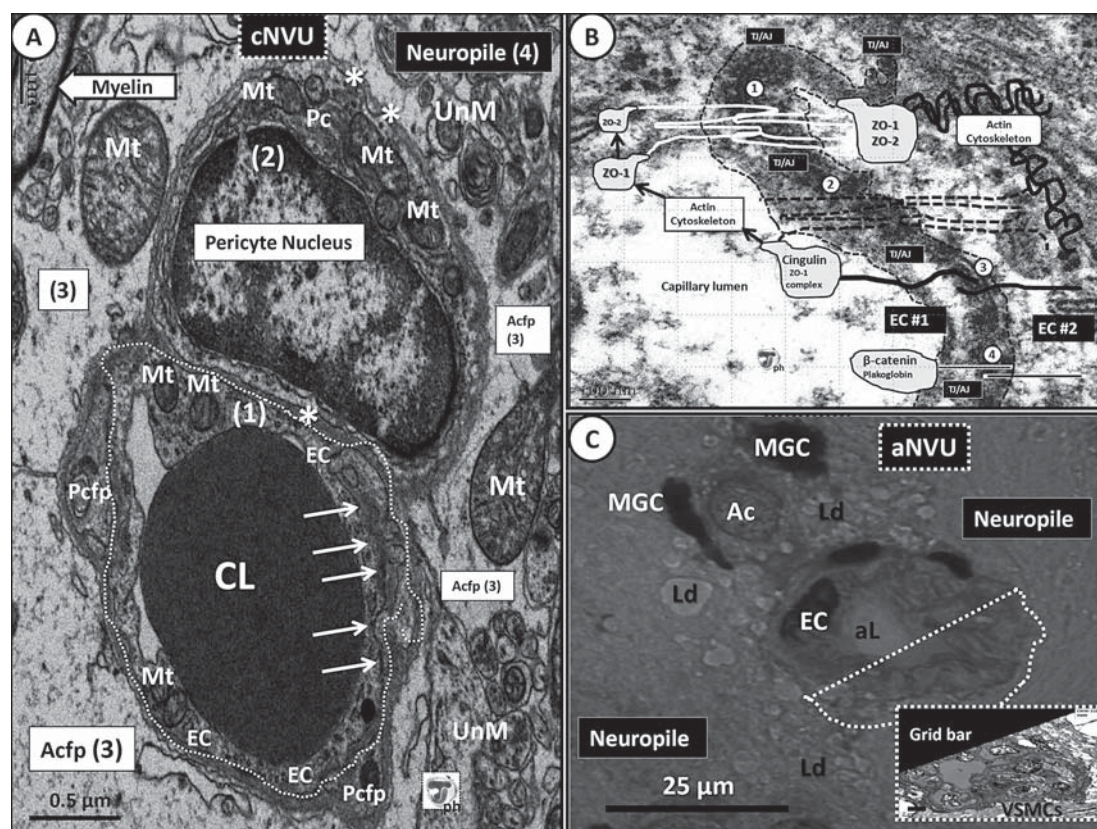
### BBB and Capillary Neurovascular Unit

Medium-sized brain arteries traverse the dura mater and branch into leptomeningeal and pial arteries, which reside on the surface of the brain in the subarachnoid space. The pial arteries then branch into penetrating intracerebral arteries and arterioles, forming the arteriole neurovascular unit (aNVU), which gradually narrow to form the capillary network and the capillary neurovascular unit (cNVU) of the brain [19]. In humans, the brain contains approximately 100 million capillaries with a surface area of 12 m<sup>2</sup>. Accordingly, almost every neuron has its own capillary, with an average distance of 8–20  $\mu$ m from capillary to neuron.

The BBB or interface within the cNVU (fig. 2A) separates the circulating blood and plasma molecules from the brain and allows for its protection from systemic neurotoxins. The BBB interface consists of a unique set of brain endothelial apical transmembrane junctional proteins termed tight junctions (TJs), which consist of requisite claudin 3 and/or 5, dispensable occludin, and the junctional adherens molecule family with essential zona occludens 1 anchoring protein to the actin cytoskeleton (fig. 2B) [20]. In addition to the TJs, there are endothelial adherens junctions (AJs), which consist of the endothelial protein vascular endothelial cadherin. Derangements of the BBB TJ/AJ complex dysfunction, attenuation, and/or loss may contribute to neurodegenerative diseases including AD, DC, VaD, MD, stroke, brain tumors, traumatic brain injury, Parkinson's disease, and multiple sclerosis.

The cNVU contains specialized ECs, extracellular matrix basement membranes (inner and outer), pericyte (Pc) (around cell)/Pc foot processes, and a corona of astrocyte (Ac) foot processes, which are intimately involved and linked to cerebral blood flow (CBF) (fig. 2A). The remainder of the cNVU comprises the neuropile with myelinated and unmyelinated neurons and the neuronal extracellular matrix. The aNVU and cNVU couples local neuronal function to the adjacent local CBF and is important for the regulation and transport of the blood-borne molecules into the brain as well as the efflux of metabolic by-products of the brain across the BBB. Importantly, the unique brain TJ/AJ complexes prevent the paracellular movement of ions, water, and water-soluble proteins. The cNVU highlights not only these cell-cell interactions but also the functional cell-matrix interactions, which support the BBB function. Additionally, AJs are linked to the actin cytoskeleton via catenins (primarily  $\beta$ -catenin) and functionally interact with TJ protein claudin 5 (fig. 2B). The AJs are important in the establishment, maturation, and maintenance of endothelial cell-cell junctions [20].





**Fig. 2.** Remodeling of the BBB TJ/AJ in diabetes. **A** Each cell comprising the normal midbrain cNVU. Magnification  $\times 5,000$ ; bar =  $0.5\ \mu\text{m}$ . EC lining the capillary lumen (CL) and bounded by a continuous white dashed line (1); inner basement membrane (single asterisk); electron-dense TJ/AJ complex (arrows); mitochondria (Mt); Pc (2) and Pc foot processes (Pcfp); outer basement membrane (double asterisk); Ac foot processes (Acfp) (3); neuropile complex (4). **B** The endothelial TJ/AJ complex of adjacent ECs in the normal cerebral microcirculation. Magnification  $\times 20,000$ ; bar =  $100\ \text{nm}$ . The TJ/AJ complex is an extremely electron-dense structure (outlined by dashes). TJs are composed of three primary spanning proteins, which are overlaid in this image: occludins (1) (solid white line) tetraspanning (nonessential); essential claudins (2) (dashed black lines) tetraspanning, and nonessential junctional adherens molecule(s) (JAM) (3) and overlapping – monospanning endothelial selective adhesion molecule(s) (3); monospanning and homophilic (overlapping bars) AJs – VE-cadherins (4) also observed in continuous capillaries in the peripheral microcirculation; platelet EC adhesion molecule(s) (4) are known to be present outside the AJ and they may have similar roles to VE-cadherins and contribute to EC stability; junctional proteins (1–4) are bound to the actin cytoskeleton of the EC to maintain stability and structure; zona occludens 1/2 (ZO-1, -2) anchor and attach occludin, claudin 3–5, and JAMs to the actin cytoskeleton; VE-cadherins are anchored and attached to the cytoskeleton primarily via  $\beta$ -catenins and plakoglobins. **C** A light microscopic image of the aNVU in the mouse model fed a Western high-fructose/high-fat diet. Magnification  $\times 100$ ; scale bar =  $25\ \mu\text{m}$ . Note the electron-dense rounded activated MGCs on either side of the Ac. Also note the arteriole with its arteriolar lumen (aL) surrounded by an EC and its thickened media consisting of vascular smooth muscle cells, which have undergone hyperplasia in the inset image from transmission electron microscopy. Importantly, note the lipid droplets (Ld) surrounding the arteriole, which were not noted in the normal diet control models.

Thus, the aNVU and cNVU provide multiple opportunities for cellular crosstalk due to the close spatial relationship and paracrine signaling between glial cells and neurons.

The brain endothelial capillaries are further characterized by the absence of fenestrations, a paucity of transcytotic vesicles (pinocytotic vesicles), and increased mitochondria as compared to peripheral systemic continuous EC capillaries (fig. 2A). BBB dysfunction occurs in both T2DM and AD resulting in the loss of electrical resistance, and abnormal leakiness of the brain capillary endothelium.

## Morphology and Function

### *Brain EC*

A monolayer of ECs lines the brain capillaries and is responsible for the maintenance of the BBB and its TJ/AJ complexes, which are located at overlapping interendothelial clefts or more complex endothelial cell-cell junctions (fig. 2). The brain ECs are characterized by TJ/AJ complexes, lack of transcytotic vesicles and pinocytosis, and expression of specialized influx transporters to facilitate the transfer of molecules to the interstitium of the brain neuropile. Thus, the endothelium (TJ/AJ complexes) is the first line of defense against systemic neurotoxins. There are at least five different pathways for molecular trafficking along the endothelium of the BBB, which includes the paracellular pathway for water-soluble agents, the transcellular lipophilic pathway for lipid-soluble agents, the transport protein pathway important for glucose, amino acids, nucleosides, receptor-mediated transcytosis of insulin and transferrin, and the adsorptive transcytosis pathway for albumin and other plasma proteins [20, 21].

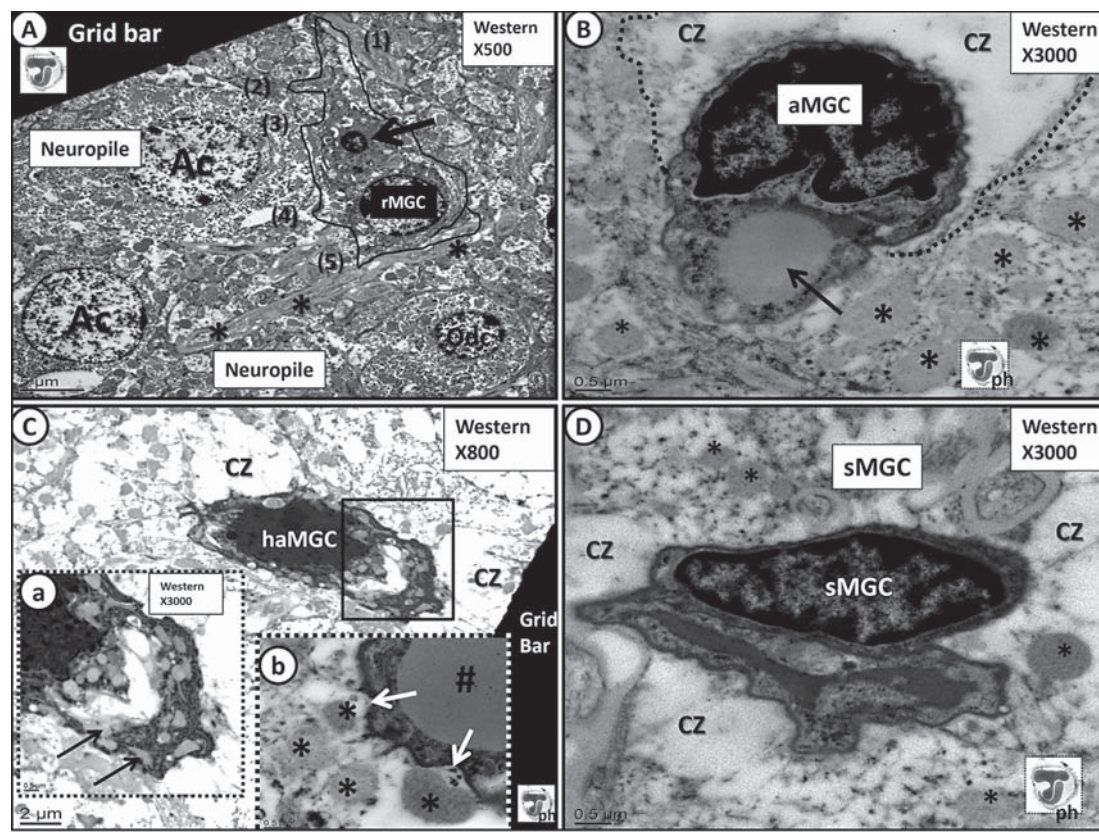
EC-derived nitric oxide (NO) is essential for the proper function of the cerebral endothelium and autoregulation of regional brain perfusion by the microcirculation. Additionally, NO is important for the proper functioning of surrounding Pcs, Acs, neurons and the cNVU. ECs are vulnerable to inflammatory cytokines and ROS of the systemic circulation in those who have the CRS and T2DM, largely consequent to reduced NO generation.

A frequent finding in the CRS and T2DM is endothelial NO synthase uncoupling, wherein excessive ROS oxidize requisite tetrahydrobiopterin (BH<sub>4</sub>) to BH<sub>3</sub> and BH<sub>2</sub>. Oxidized BH<sub>4</sub> results in endothelial NO synthase uncoupling, reduced NO bioavailability, endothelial dysfunction and a proconstrictive, pro-oxidative, proinflammatory, prothrombotic state. This environment activates local matrix metalloproteinase(s), which induces injury of the TJ/AJ complex leading to EC dysfunction and leakiness of toxins into the neural interstitium [22]. Leakiness of the TJ/AJ complex negatively affects cells in the neuropile resulting in microglia activation (fig. 3) and inflammation, Ac dysfunction with membrane ruffling (fig. 2) and migration, oligodendrocyte dysfunction with accompanying increased A $\beta$  deposition of senile plaques, and misfolding of tau proteins in microtubules and neurofibrillary tangles in AD, which may result in neurodegeneration in DC and AD.

### *The Brain Pc Cell*

Pcs play a key role in the development of the cerebral microvasculature [23–28]. The brain and retina have the highest percentage of endothelial Pc coverage when compared to other microvessels. The Pc or ‘around cell’ encompasses the EC abluminally (fig. 2A). They are present in precapillary arterioles, capillaries, and postcapillary venules. Importantly, brain Pcs maintain endothelial vascular integrity preventing abnormal permeability and brain immune cell infiltration. They are essential to the development of TJ proteins as well as the maintenance and stability of the endothelium and its TJ/AJ complexes. Further, cell-cell communication (crosstalk) of Pcs and ECs occur by direct contact via their shared





**Fig. 3.** Microglia phenotype remodeling in the mouse model fed a Western high-fructose/high-fat diet. **A** A ramified microglial cell (rMGC) (violin shaped; outlined in black) with a lysosome (arrow), which is rarely observed in the Western models. Note the pair of astrocytes (Ac) and one oligodendrocyte (Odc) in immediate contact with a thickened dystrophic myelin sheath surrounding a neuronal axon (asterisks). Magnification  $\times 500$ ; scale bar = 5  $\mu\text{m}$ . **B** An activated MGC (aMGC). Note the lipid-like homogeneous inclusion body – granule (arrow) within the cytoplasm. Importantly, note the multiple abnormal lipofuscin-like granules surrounding the aMGC (asterisks). The aMGCs seem to frequently have an Ac clear zone (CZ) surrounding their outer edges. Magnification  $\times 3,000$ ; bar = 0.5  $\mu\text{m}$ . **C** A highly activated MGC (haMGC) with an extensively activated endoplasmic reticulum surrounding small lipid-like inclusion granules. Magnification  $\times 800$ ; bar = 2  $\mu\text{m}$ . **Inset a** is a higher magnification of the boxed-in region. Magnification  $\times 3,000$ ; bar = 0.5  $\mu\text{m}$ . **Inset b** illustrates spikes tethering lipofuscin-like granules (asterisks) and displays macropinocytosis of lipofuscin-like material and cleft/pouch (arrows) on the plasmalemma of an aMGC with an inclusion body-granule (#). **D** A senescent MGC (sMGC). Note the very small amount of cytoplasm and loss of organelles, which may be indicative of cytorrhesis. Magnification  $\times 3,000$ ; bar = 0.5  $\mu\text{m}$ .

basement membrane, peg sockets, and paracrine signaling. Pcs and ECs share a common basement membrane and are also secured by N-cadherins, fibronectin, connexins, and various integrins [24]. Additionally, Pcs induce the synthesis of occludin and claudin in the EC TJ/AJ complex via the synthesis and release of angiopoietin 1. Pcs also contribute to the polarization of Ac end feet surrounding the NVU [23]. ECs signal Pcs by synthesizing and secreting platelet-derived growth factor  $\beta$  (PDGF- $\beta$ ) to signal the Pc-specific receptor (PDGFR- $\beta$ ), which is important for Pc proliferation, migration, and recruitment of Pc to the endothelium. The *Pdgfrb* knockout mouse model is lethal and *Pdgfrb* heterozygous mice reveal structural abnormalities of the TJ/AJ complex [24, 25]. Pcs are capable of constricting the cNVU and control neurovascular functions necessary for neuronal structure and



function [25]. Heterozygous *Pdgfrb*<sup>+/-</sup> mice manifest an age-dependent Pc loss, which results in reduced brain microcirculation with reduced CBF leading to hypoxia, BBB dysfunction, and leakiness of cerebral capillaries. Importantly, these pathways cause neuronal dysfunction, injury, and eventual neurodegeneration [23, 24]. Excessive ROS induced by hyperglycemia and other metabolic toxicities may result in Pc migration, dysfunction, and ultimately apoptosis [23–29]. Recently, an inhibitor of mitochondrial carbonic anhydrase (toprimate) was reported to rescue Pcs from high glucose-induced oxidative stress and apoptosis [26].

In summary, brain Pcs are an essential cellular component of the cNVU involved in the regulation of CBF, BBB function, and stabilization of endothelial structure and function. Pcs may also have pleiotropic functions as well as stromal and regeneration function [28]. Interestingly, brain mesenchymal stem cells reside in perivascular compartments or niches located primarily at vascular branching points, which have characteristics associated with Pcs [30]. These perivascular cells share both a mesenchymal and Pc phenotype, which have the potential to differentiate into mesodermal and neuroectodermal progeny [30]. Pcs may become dysfunctional, attenuated, or lost due to their vulnerability to oxidative stress and inflammation associated with the CRS and T2DM.

#### *The Brain Ac Cell*

Acs are critical for the induction and maintenance of cNVU, BBB, TJ/AJ complexes, providing a vast communicating autocrine and paracrine network between the cNVU and aNVU and neurons (neurovascular coupling). Additionally, Acs are essential in fluid balance, glycogen storage for the energy supply (glucose-lactate) for neurons, regulation of glutamate reuptake, provision of antioxidant production via glutathione (GSH), protection of neurons from excessive ROS resulting in neurodegeneration, gliosis as a response-to-injury mechanism, and maintaining neuronal plasticity [31–33].

Acs are the most abundant glial cell type in the brain (outnumbering neurons by 5-fold), they function as a syncytium of highly interconnected cells, and are important in regulating the maintenance and repair of the BBB and its TJ/AJ complexes as well as neuronal support and plasticity. They are an integral part of the cNVU and aNVU and physically link the NVU to neurons via their foot processes of the NVU and their tripartite synapses with neurons (fig. 2A) [31]. The connectivity of Acs with the NVU and neurons place them in a unique position to take up glucose from the capillaries of the NVU and function as a carbohydrate reservoir by storing glycogen. In turn, Acs supply energy metabolites to a vast number of different neuronal elements in the gray and white matter of the brain. This unique ability allows Acs to supply energy via glycogenolysis and produce glucose and even lactate during periods of high neuronal activity and/or hypoglycemia [31]. The Ac foot processes (fig. 2A, C) contain specialized features important for volume and ion regulation, which includes the water channel aquaporin 4 and the potassium channel (Kir4.1). Importantly, aquaporin 4 and the potassium channels are dependent on the polarizing basement membrane (basal lamina) extracellular matrix anchoring protein agrin [31]. Several glial-derived factors of Acs are secreted including transforming growth factor  $\beta$  (TGF- $\beta$ ), glial-derived neurotrophic factor, basic fibroblast growth factor, and angiopoietin 1, which contribute to the BBB phenotype in the brain [31]. Thus, the Ac is capable of molecular crosstalk with the endothelium (Ac-EC interactions) and the Pc (Ac-Pc interactions) [31]. Acs are an important component of the NVU antioxidant defense system through the regulation of extracellular glutamate concentrations via glutamate transporters and uptake of glutamate and production of cellular antioxidant compounds [32]. Acs are an important source of the antioxidant GSH via a sodium-independent exchange for glutamate via the transport system  $X_c^-$  to protect neurons. GSH is known to decrease with aging in human brains, and the loss of this antioxidant defense mech-

anism may be one of the important contributors to the increased risk of aging in the development of CID, DC, and AD.

In addition to structural support and communication of the NVU to neurons of the neuropile, Acs support trophic functions, metabolic support, and assist in neuronal plasticity. Furthermore, Acs are capable of reactive gliosis, which is associated with glial fibrillary acidic protein-positive staining in a response-to-injury mechanism. Gliosis involves the initial migration of macrophages and local brain microglia to the injured site (microgliosis) followed by oligodendrocyte migration, which contributes to remyelination, followed by the migration with plasma membrane ruffling and accumulation of Acs, i.e. astrogliosis, creating a glial scar within the brain. Neurotoxic injuries occur in the presence of chronic multiple metabolic toxicities that accompany the CRS and diabetes or ischemia reperfusion injury (as in vascular ischemia and/or stroke in VaD). Importantly, parenchymal arteriole vascular smooth muscle cells and Pcs, along with cNVU Pcs, are in direct contact with functionally active neurons via the connecting ability of Acs. Thus, Acs are essential for the multiple complex paracrine signaling from these neurons to induce the vasodilatation that is required to increase CBF that is known to result in the functional hyperemia (CBF coupling to neural activity) associated with increased neuronal activity [33]. Therefore, the CRS and to a greater extent T2DM result not only in brain atrophy but also the uncoupling of CBF and neural activity [34].

### **VaD, AD, MD and DC**

VaD is an important sequelae of the CRS and T2DM, and VaD and AD may develop concurrently, referred to as MD. MD may be a consequence of the shared metabolic and vascular risk factors. For example, neuropathological data reveal that 30% of patients with a clinical diagnosis of AD were found at postmortem to also have cerebrovascular disease (VaD), and patients with VaD were found at postmortem to show evidence of AD pathology. The distinction between these dementias is thus not complete, perhaps because they share common abnormalities of the endothelial TJ/AJ complexes within the BBB (table 1) [35–37].

The hypothalamic pituitary adrenal (HPA) axis is dysfunctional in obesity, CRS, and T2DM, with resultant excess glucocorticoids, mineralocorticoids, and chronically increased sympathetic tone [1, 38]. Recently, our laboratory has been able to demonstrate that C57BL/6 mice fed a high-fructose (55%)/glucose (45%) and a high-fat 'Western diet' developed obesity and elevated mineralocorticoids [39] and adrenal cortical hyperplasia [unpubl. data]. The above observations tend to support a dysfunctional HPA axis with excess stimulation of the adrenal cortex by anterior pituitary-derived adrenocorticotrophic hormone, which may result in hyperplasia of the adrenal cortex. This hyperplasia may develop because of HPA axis dysfunction associated with obesity-related IR, hyperleptinemia, and LR [39]. When the HPA axis-central feedback is impaired, there is associated memory impairment, possibility reflecting hippocampal dysfunction [38].

### **Brain Renin-Angiotensin-Aldosterone System in Obesity, CRS, and T2DM**

The brain locally forms and degrades angiotensin peptides, independent of the systemic circulation [40]. The angiotensin receptor subtypes AT<sub>1</sub>R, AT<sub>2</sub>R, and AT<sub>4</sub>R are present in the brain, and AT<sub>4</sub>R is identical to the insulin-regulated aminopeptidase, which is often referred to as the AT<sub>4</sub>R/insulin-regulated aminopeptidase receptor. The brain renin-angiotensin-aldosterone system (RAAS) is important in neural function homeostasis and plays a role in normal memory, consolidation, and retrieval of information; RAAS dysfunction is also an

important component in the development of CID [40–47]. Excessive RAAS activation has damaging effects resulting in impaired cognitive function. These chronic effects induce cerebrovascular remodeling, vascular inflammation via Ac-derived TGF- $\beta$ , oxidative stress/ROS via activation of NADPH oxidase, Ac senescence due to increased ROS and aldosterone synthesis/secretion, and an impairment of CBF resulting in neurodegeneration and cognitive impairment [38].

Enhanced activation of AT<sub>1</sub>R by angiotensin II, and of the mineralocorticoid receptor by aldosterone and glucocorticoids increases BBB permeability, neuroinflammation, oxidative stress, and Ac dysfunction while decreasing CBF [41]. Indeed, angiotensin receptor blockers have been shown to be associated with a significant reduction in the incidence and progression of AD and dementia compared to other antihypertensive treatments [47].

### Cardiac and Renal Contributions to DC

DC, VaD, MDs, and AD have similar shared environmental and genetic risk factors (e.g. aging, hypertension, diabetes, smoking, and APOE  $\epsilon$ 4), which are associated with toxic RAS, inflammatory, and metabolic derangements related to the CRS. Cardiac abnormalities may contribute directly to DC through multiple mechanisms, including decreased brain perfusion consequent to dysfunctional myocardium with diastolic dysfunction (diabetic cardiomyopathy), cardiac arrhythmias, stroke and microemboli, myocardial infarction, and reduced systolic function. All of the above may contribute to systemic hypoperfusion and disrupt cerebral perfusion and CBF. Importantly, the brain is known to possess an autoregulatory mechanism for maintaining CBF; however, conditions resulting in reduced cardiac output can overwhelm the CNS autoregulatory mechanism. The diabetic cardiomyopathy observed in CRS and T2DM may be associated with cognitive impairment, dementias, and DC due to direct myocardial dysfunction, decreased cardiac output, hypoperfusion, and the associated decreased cerebral perfusion and CBF [48–50].

#### *Renal Contributions*

Renal disease is a major component of the CRS [51, 52], and independently, renal disease is associated with diabetes, hypertension, and hyperlipidemia as occurs in the CRS. The progression of CRS-associated renal dysfunction to chronic kidney disease is linked to increases in oxidative stress, inflammation, chronic anemia, vascular calcification, and increased homocysteine, uric acid, and parathyroid hormone [53]. These latter substances are neurotoxins and associated with increased risk of AD, VaD, MDs, and DC [52, 53].

### Mitochondria and Oxidative Stress Roles in DC

Oxidative stress has been implicated in the pathology of several chronic age-related diseases, and dysfunctional mitochondria contribute to brain oxidative stress in these diseases including CRS, T2DM, and AD. Defective mitochondria, with identifiable functional and structural abnormalities, are known to occur upstream or antedate the development of clinical AD. Mitochondria are the major source of energy in the CNS, providing the energy currency (adenosine triphosphate) for continuous synaptic transmission of information from one cell to another. In health, neurons and glial cells have sufficient innate antioxidants to neutralize mitochondrial production of ROS. However, in age-related diseases such as CRS, T2DM, AD, and DC, the innate antioxidant defense is depleted, with a resultant increase in toxic ROS generation [54, 55].



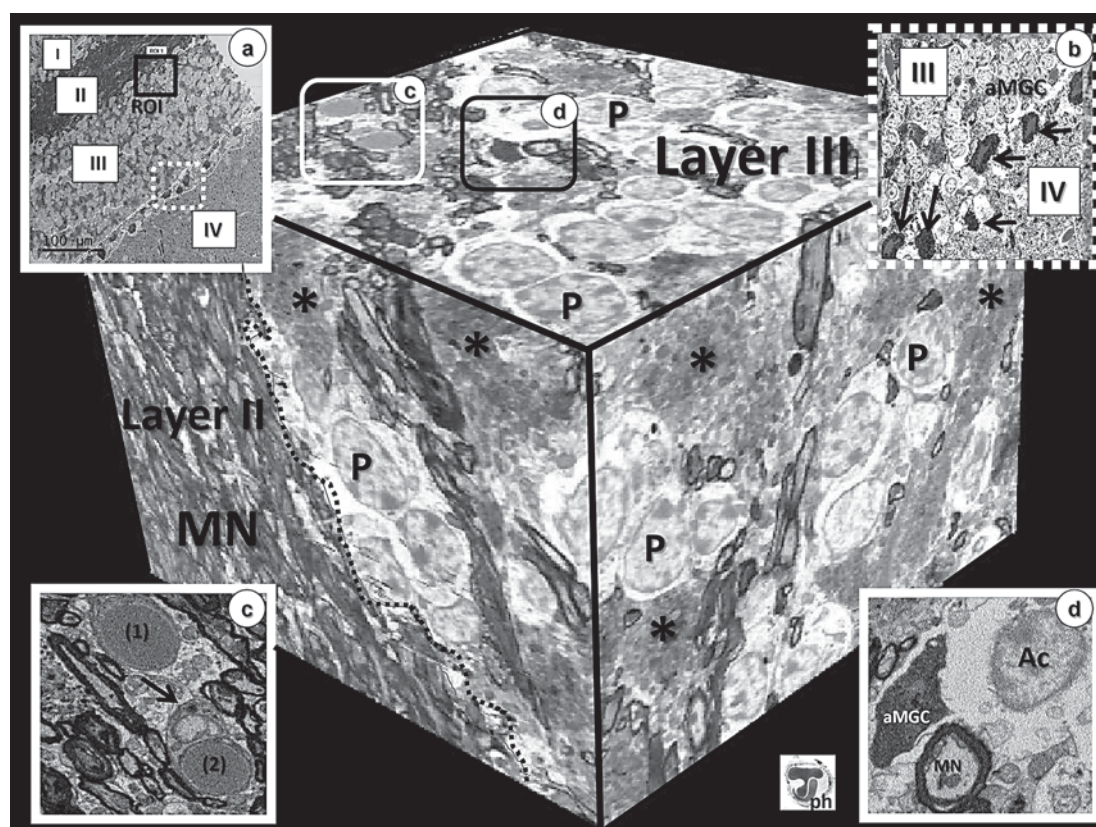
### Role of Low-Grade Chronic Inflammation in DC: Microglia

T2DM and AD each have a significant inflammatory component and there may be peripheral and central (brain) inflammatory synergy between T2DM and AD, which might result in DC [56]. T2DM may increase the development of AD via several mechanisms, which include brain IR, impaired insulin receptor and insulin-like growth factor signaling, glucotoxicity, cerebrovascular injury/hypoxia, peripheral chronic inflammation and brain inflammation associated with an advanced glycation end product (AGE)/receptor for AGE (RAGE) interaction and a RAGE-driven inflammatory synergy [56].

The AGE/RAGE interaction, which generates excessive ROS and in turn activates nuclear factor- $\kappa$ B and downstream cytokines in both the periphery and brain, may be a central player in the inflammatory synergy associated with T2DM, AD, MDs, and DC. RAGE-driven inflammatory synergy associated with subsequent inflammatory responses in the periphery and brain is detrimental to cognitive function [56]. In health, the periphery and brain are segregated from one another via the intact endothelial BBB of the NVU. However, if the BBB TJ/AJ complex of the NVU is attenuated or lost as in T2DM and AD, then the AGE/RAGE interaction may result in a self-perpetuating cascade. Shared cytokines and chemokines (IL-1 $\beta$ , IL-6, TNF- $\alpha$ , and macrophage colony-stimulating factor) may pass via the paracellular regions when the BBB TJ/AJ complexes have lost their integrity. Likewise, ligands for RAGE including high-mobility group box 1 protein, S100B, S100A8/9/12, and AGE from the brain may pass into the periphery and activate RAGE. Since RAGE expression is increased by its available ligands from either the brain or periphery, a vicious cycle may ensue [56]. These observations implicate AGE-RAGE interaction, peripheral macrophage or central perivascular macrophage, and specifically microglia cell(s) (MGC).

MGCs represent the resident macrophage of the CNS and are responsible for the innate immunity of the brain participating in both innate and adaptive immune responses [56–58]. Importantly, MGCs may be increased and their morphologic phenotype remodeled to an activated, highly activated, or senescent MGC phenotype (fig. 3) in a response-to-injury mechanism due to the underlying injuries of neurotoxins, oxidative stress, excessive A $\beta$  or lipofuscin accumulation, glucotoxicity, pathogens, traumatic brain injury, and aging. Additionally, other multiple neurotoxins lead to NVU dysfunction of the endothelial BBB with attenuation or loss of the TJ/AJ complexes. Ramified MGCs are capable of undergoing morphologic and functional remodeling and are capable of synthesizing and secreting the antioxidative, anti-inflammatory, and antiatherosclerotic cytokine IL-10. Ramified MGCs have multiple elongated and ramified dendritic cell processes with a close spatial relationship to neurons and other glial cells, and continuously survey the neuropile for injury or breakdown of cellular excess metabolic stimulation and normal mild neurodegeneration (fig. 3A). When MGCs are activated, they are known to become amoeboid-like, rounded in morphology, and referred to by some as the M1 phenotype with loss of elongated cytoplasmic processes and their close spatial relationship to neurons (fig. 2B–D). With this morphological remodeling they also change their function and become cells that synthesize and secrete additional damaging cytokines and chemokines and lose their capacity to synthesize and secrete IL-10 as well as generating increased ROS. Recently, our lab has demonstrated increased morphologic remodeling of ramified MGCs in the cerebral cortex of Western diet-fed mice to the activated MGC phenotype [unpubl. data] (fig. 3, 4).

Importantly, ramified MGCs of the brain's innate immune system may be neuroprotective (the cleaners, sweepers, and electricians of the brain). They are capable of scavenging damaging proteins (as occurs in the amyloid cascade/neuroinflammation hypothesis of AD), protecting the brain from pathogenic infectious organisms, and the production and secretion of neurotrophic factors such as insulin-like growth factor 1, TGF- $\beta$ , brain-derived neuro-



**Fig. 4.** 3View cube of layers II and III of the cerebral cortex in Western diet. This image illustrates a cube image using 3View technology, which was generated from field emission scanning electron microscopy. Layers II (external granular layer) and III (pyramidal layer) are the main focus of this cube. Note the pyramidal neuronal nuclei (P) in layer III. Also, note regions of unmyelinated neurons (asterisks) in layer III. **Inset a** depicts the region of interest (ROI) that was examined to create the cube image, the white boxed-in **inset b** and cortical layers I–IV. **Inset b** demonstrates the activated microglia cells (aMGC) (arrows) found between pyramidal layer III and the internal granular layer IV from the white boxed-in dashed lines in **inset a**. **Inset c** is an exploded image from the cube image; note capillary (1) and (2) with an arrow depicting the encircling capillary Pc. **Inset d** illustrates an Ac alongside an aMGC and an electron-dense myelinated neuron (MN).

trophic factor, and nerve growth factor. Additionally, MGCs are capable of diverting noxious and harmful substances away from neurons and aid in the synaptic pruning and neurogenesis [57]. Recently, it has been demonstrated that aging or senescent MGCs (fig. 3D) change their morphological phenotype from one of being ramified (branched) to one that is amoeboid, and their function is altered to one of excessive damaging cytokines and ROS production, which may result in damage and neurodegeneration [58].

### Therapeutic Options in DC

Current therapeutic options available to prevent or delay the progression of DC, MD, VaD, and AD (table 2) should comprise global risk reduction of the multiple metabolic toxicities, which include weight reduction and exercise, improvement of peripheral and central IR, LR, oxidative stress, and inflammation. Modifiable risk factors include midlife obesity, lack of

**Table 2.** Possible therapeutic options for the treatment of DC

I	Insulin resistance	Improvement of insulin sensitivity (a) Metformin and TZDs (PPAR- $\gamma$ agonists) (b) GLP-1 agonists (extendin-4) (clinical trials have been initiated) (c) Dipeptidyl peptidase-4 antagonists may be of benefit (d) Intranasal insulin (clinical trials have been initiated) (e) Glycogen synthase kinase-3 inhibitors (preclinical trials have been initiated)
II	Hypertension control	(a) RAAS blockade Angiotensin-converting enzyme inhibitor(s) Angiotensin receptor blocker(s) Mineralocorticoid receptor blockade (b) $\beta$ -Blockade (affecting not only hypertension but also increased sympathetic tone)
III	Hyperglycemia	Oral diabetic medications and insulin. Note that one should be careful not to induce hypoglycemia as this may contribute to abnormal remodeling and be detrimental to the brain
IV	Hyperlipidemia Dyslipidemia	HMG-CoA reductase inhibitors – statins: decrease cardiovascular/cerebrovascular events/stroke, which may have positive effects on VaD, MD and DC; however, research is unclear regarding statins and cognitive impairments and dementia. Importantly, hypercholesterolemia accelerates A $\beta$ and tau pathologies
V	Hyperuricemia	As a marker of oxidative stress. Xanthine oxidase inhibitors may be of future importance
VI	Obesity and lack of exercise	Lifestyle modification: nutritional modifications and increased physical exercise that result in weight loss. Also consider mental exercise
VII	Oxidative stress	Antioxidant therapies: (a) Potent antioxidant mono- and combination therapies [55] (b) Intravenous STS as a novel modality. Calciphylaxis success clinically [62, 63]. Potent antioxidant and chelator of cation excess (calcium, iron, copper, and aluminum) (c) Hydrogen sulfide (H <sub>2</sub> S) restoration: decreased in brain of AD patients and decreased in serum of T2DM patients. H <sub>2</sub> S is a potent vasodilator and antioxidant [62, 63]
VIII	Improvement of neurotransmitter deficiencies	(a) Acetylcholinesterase inhibitors: IR and AD can contribute to a decrease in acetylcholine (b) NMDA receptor antagonists Comment: slow worsening of symptoms of 6–12 months' duration; only effective in approximately half of patients [60, 61]
IX	Inhibition of senile plaques and neurofibrillary tangles	A $\beta$ passive immunotherapy: recent discouraging news; however, this treatment will be reevaluated at earlier time points in the development of AD [60]

Note that therapeutic options I–VII are directly related to the CRS construct. TZDs = Thiazolidinediones; PPAR = peroxisome proliferator-activated receptor; NMDA = N-methyl-D-aspartate.



physical and mental exercise, obesity, IR, excessive ROS, the CRS, T2DM and cerebral vascular disease.

Cholinesterase inhibitors have been the mainstay in the treatment of AD for over a decade. However, they usually lose their effects within 6–12 months, have a positive effect on only 50% of patients treated and do not slow the progression of the disease in the transit from home care to institutionalized care [59, 60]. Mitochondrial dysfunction plays a major role in the development of T2DM and neurodegenerative AD, and undoubtedly plays a major role in the development of DC. Therefore, the use of mono- or multiple antioxidants may prove useful in the delay of progression of CID and DC. Some have advocated using a combination of antioxidants, which includes creatine, acetyl-L-carnitine, coenzyme Q10 (MitoQ), vitamin E (MitoVitE),  $\beta$ -lipoic acid, N-acetyl cysteine, and small peptide antioxidants to block the excess ROS in AD [54]. While this approach has been positive in small clinical studies, it remains to be seen if these results will translate to larger clinical trials.

#### *Future Directions and Novel Therapies*

Intravenous sodium thiosulfate (STS) is a novel and effective therapy for calciphylaxis (calcific uremic arteriopathy) [61, 62], utilizing its potent antioxidant potential of having two unpaired electrons, which are readily donated and may be of help in delaying the development and/or progression of CID, AD, and DC. Also, STS may restore hydrogen sulfide ( $H_2S$ ), which is known to be decreased in AD brain tissues and in the serum of patients with T2DM. Importantly, STS may also be beneficial due to its chelation potential of excessive cations such as iron, copper, calcium, and aluminum, which may mediate cellular damage by abnormal metal interaction with A $\beta$  and the association of metal-mediated oxidative stress in the treatment of CID, AD, and DC in the coming years. Because the development and progression of CID, AD, and DC is multifactorial, a 3-hit drug with very few side effects (osteoporosis with long-term therapy and mild acidosis acutely) and now used in the treatment of calciphylaxis may slow the development and progression of CID, AD, and DC associated with T2DM.

Incretin hormones such as glucagon-like peptide 1 (GLP-1) have anti-inflammatory properties, are neuroprotective, and reduce appetite in addition to stimulating insulin secretion, and are being investigated as therapies for AD [63]. GLP-1 mimetics such as extendin-4 used clinically for the treatment of T2DM are currently being used in a clinical trial by the National Institute of Aging. The strong comorbidities between T2DM and the neurodegeneration observed in AD along with the neuroprotective role of GLP-1 make it a likely candidate, and in due time we will know the outcome of its clinical effectiveness. The GLP-1 receptor is abundantly expressed in many parts of the brain, which includes the hypothalamus (important in the HPA axis previously discussed), hippocampus (with its early involvement with CID in T2DM, AD, and DC), and the cerebral cortex [64]. In C57BL/6 mouse controls, GLP-1-positive cells were identified in the cortex and hippocampus. These cells were decreased significantly along with the proglucagon mRNA in the obese *ob/ob* mouse model of obesity and IR [64]. Of great interest was the finding of the proglucagon gene and the secretion of GLP-1 in a cyclic adenosine monophosphate-dependent manner in MGCs. Importantly, MGCs may be a central brain source for GLP-1 secretion, and in insulin-resistant conditions the expression and secretion of GLP-1 and mRNA expression of proglucagon are decreased, which heightens the importance of MGC activation in excess nutrition, obesity, IR, and T2DM and its relation to early neurodegeneration [63]. Accordingly, dipeptidyl peptidase 4 inhibitor therapy may have beneficial effects to attenuate the multiple toxicities that promote DC in diabetic patients.

IR in the brain is associated with CID, AD, and DC. Intranasal insulin administration allows insulin to be absorbed peripherally via the nasal mucus membranes and hence travels along the olfactory and trigeminal perivascular channels along with slower olfactory nerve axonal transport pathways. Small pilot studies have demonstrated improvements in retention of

delayed verbal memory, improved attention, preserved caregiver-rated functional ability, and suggest that intranasal insulin may be a novel approach for the treatment of neurodegenerative disorders without adverse events [65].

Our laboratory has recently been able to utilize 3View® technology to observe the three-dimensional relationship between neurons, glial cells, organelles, and extracellular matrix in the brain. This new technology may help unravel some of the mysteries of brain remodeling and aid in the knowledge of how overnutrition affects the ultrastructural remodeling in the brain (fig. 4).

In summary, CRS, obesity, and T2DM are pandemic, and associated with increased risk of VaD, AD, MDs and DC. Concurrently, there are multiple metabolic toxicities, which promote oxidative stress and inflammation. These effects result in an endotheliopathy (endothelial dysfunction), which leads to diabetic cardiomyopathy and diabetic nephropathy, and may also contribute to subsequent brain remodeling as time progresses. IR and ROS are closely involved at each turn in the development of end organ remodeling and disease, which includes DC.

Patients with DC may be in ‘search of lost times’, confused, and virtually locked and lost within the confines of their own brain. Caregivers and researchers should consider the terminology of DC with ‘new eyes’ and develop a better understanding of this burgeoning entity.

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Authors report no conflict of interest.

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