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Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums

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Abstract

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Considerable overlap has been identified in the risk factors, comorbidities and putative pathophysiological mechanisms of Alzheimer disease and related dementias (ADRDs) and type 2 diabetes mellitus (T2DM), two of the most pressing epidemics of our time. Much is known about the biology of each condition, but whether T2DM and ADRDs are parallel phenomena arising from coincidental roots in ageing or synergistic diseases linked by vicious pathophysiological cycles remains unclear. Insulin resistance is a core feature of T2DM and is emerging as a potentially important feature of ADRDs. Here, we review key observations and experimental data on insulin signalling in the brain, highlighting its actions in neurons and glia. In addition, we define the concept of 'brain insulin resistance' and review the growing, although still inconsistent, literature concerning cognitive impairment and neuropathological abnormalities in T2DM, obesity and insulin resistance. Lastly, we review evidence of intrinsic brain insulin resistance in ADRDs. By expanding our understanding of the overlapping mechanisms of these conditions, we hope to accelerate the rational development of preventive, disease-modifying and symptomatic treatments for cognitive dysfunction in T2DM and ADRDs alike.

Type 2 diabetes mellitus (T2DM), dementia due to Alzheimer disease (AD), and AD-related dementias (such as mild cognitive impairment (MCI), vascular contributions to cognitive impairment and dementia, Lewy body diseases, and frontotemporal dementias)[1,2] are among the most common, costly and disabling conditions in the industrialized world. Until recently, AD and related dementias (ADRDs) and T2DM were thought to have little obvious relationship to one another, apart from an association with stroke.

However, a growing body of epidemiological and molecular evidence now suggests that a considerable overlap in risk, comorbidity and pathophysiological mechanisms exists across these conditions[3–19]. The phenomenon of insulin resistance is essential to our understanding of this overlap. Insulin resistance has long been recognized as a central feature of T2DM, but research from the past few years has shown that it also occurs in the brains of individuals with ADRDs, even in the absence of concurrent T2DM. In this Review, we describe the actions of insulin in the body and brain, offer a definition of brain insulin resistance as it might occur in T2DM and ADRDs and highlight key clinical and preclinical data that support the association of these two conditions, as well as incongruous data that suggest that they are independent. To conclude, we propose questions aiming to expand our understanding of extrinsic (that is, systemic) and intrinsic processes that mediate insulin resistance in the brain. We hope that this knowledge will lead to improved brain health — including improved cognitive function — in individuals with T2DM and ADRDs.

Insulin action

Human insulin is a 51-amino acid peptide hormone produced by pancreatic β-cells. Its synthesis and release into blood is stimulated by an increase in the level of circulating blood glucose[20,21], although changes in the levels of other substances — including amino acids, acetylcholine, cholecystokinin and incretin hormones — also stimulate its release. Insulin acts in tissues throughout the body. Its best−known role is to maintain plasma glucose within a physiological range by promoting glucose uptake (especially by skeletal muscle) and inhibiting glucose production and release by the liver. Insulin also functions as an anabolic

hormone that promotes fatty acid and amino acid uptake, energy storage and cellular growth. Conversely, insulin inhibits catabolic processes such as gluconeo-genesis, glycolysis, lipolysis and proteolysis. Diabetes mellitus is characterized by elevated blood glucose levels that result from insufficient insulin production or insulin activity. Type 1 diabetes mellitus is typically caused by autoimmune destruction of β-cells, whereas T2DM results from a failure of β-cells to produce enough insulin to overcome systemic insulin resistance, usually associated with obesity, inactivity and ageing. T2DM, the most common form of diabetes mellitus, will be the focus of this Review.

Insulin signalling and diverse cellular actions

Insulin elicits its cellular actions by binding receptors present on most cells. When insulin binds the extracellular α-subunits of insulin receptors, it induces the dimerization of the intracellular β-subunits, which activates intrinsic tyrosine kinases and causes receptor autophosphorylation. Insulin-like growth factor 1 (IGF1) also binds and activates insulin receptors, and both insulin and IGF receptors can initiate many of the same trophic actions[22,23].

In the canonical insulin signalling pathways[24] (FIG. 1), autophosphorylated β-subunits of insulin receptors recruit molecular adaptor proteins belonging to the insulin receptor substrate (IRS) family, as well as the SHC-transforming family of proteins. Of these IRS family proteins, IRS1 and IRS2 are the best characterized, most widely distributed and most relevant to the classic metabolic actions of insulin. Although IRS1 and IRS2 have overlapping signal transduction activity, IRS1 is especially important in skeletal muscle, adipose tissue and the cerebral cortex whereas IRS2 is important in the liver and hypothalamus. The tyrosine kinase activity of insulin receptors phosphorylates tyrosine residues on IRS1 or IRS2, which activates these keystones of insulin action and stimulates signalling via the AKT pathway. Recruitment of SHC proteins by insulin receptors also leads to activation of the RAS–RAF–MAPK (mitogen−activated protein kinase) pathway.

The insulin–IRS–AKT pathway is of special interest in T2DM as it mediates the translocation of the major glucose transporter, GLUT4 (also known as SLC2A4), from intracellular vesicles to the plasma membrane of muscle and adipose cells[25], which facilitates diffusion of glucose into these cells, thereby reducing blood glucose. By contrast, in the liver[26], glucose enters and is released from hepatocytes by GLUT2, which is not regulated by insulin. However, insulin stimulates glycogen synthase in the liver to store glucose as glycogen and inhibits glycogen phosphorylase, thus inhibiting glycogenolysis and glucose release. These actions are the major determinants of whole-body glucose homeostasis.

Beyond its glucoregulatory actions in muscle, adipose and liver tissue, the insulin–IRS–AKT pathway mediates a host of downstream processes in all cell types. This pathway regulates phosphorylation of many intracellular proteins, including serine/threonine−protein kinase mTOR, glycogen synthase kinase 3 (GSK3), cAMP-responsive element-binding protein (CREB), filamin A and nitric oxide synthases, and thus is involved in a multitude of processes, including DNA replication and cell cycle activity, protein synthesis, cell survival, metabolism, angiogenesis, potassium uptake, lipid modification and autophagy.

The MAPK pathway is the other key signalling pathway activated by insulin. This pathway controls a variety of transcription factors and elements, such as CREB and proto-oncogenes c-Myc (MYC) and c-Fos (FOS), and helps to regulate the transcription, translation and post-translational modifications of many important proteins, including other growth factors, receptor genes and matrix−modifying proteins. Activation of the insulin–IRS–AKT and MAPK cascades does not necessarily occur in concert, especially under pathophysiological conditions, in which one pathway might be activated while the other is not[27]. Furthermore, although these signalling mechanisms potentially occur in all cell types, the effects of insulin vary widely across different cells and tissues.

Insulin and the brain

Insulin receptors are expressed on all cell types in the brain, although substantial variation in expression levels exists between regions. Within the brain, insulin receptor density is highest in the olfactory bulb, hypothalamus, hippocampus, cerebral cortex, striatum and cerebellum[28–31]. The widespread distribution of these receptors suggests that insulin signalling has important and diverse roles in the brain (FIG. 2).

Sources of insulin in the brain

Insulin levels in cerebrospinal fluid (CSF) are much lower than in plasma[32,33], but these levels are correlated, indicating that most insulin in the brain derives from circulating pancreatic insulin. Insulin enters the brain primarily via selective, saturable transport across the capillary endothelial cells of the blood–brain barrier (BBB)[34–38]. Transport is affected by a number of factors, including obesity, inflammation, glycaemia, diabetes mellitus and levels of circulating triglycerides[39]. In humans, the CSF:serum ratio of insulin levels is reported to be reduced in the presence of whole−body insulin resistance[40], as well as with increasing age and in disease states such as AD[41,42]. One possible explanation is decreased transport of insulin across the BBB.

Some controversial work has suggested that insulin is also synthesized *de novo* in the brain. Insulin mRNA expression has been reported in selected brain regions in rats and mice, and production of insulin peptide has been described in primary cultured neurons from rats, but not in glia[43–48]. However, the specificities of these assays have been questioned, and other studies have failed to demonstrate the presence of insulin mRNA or protein in appreciable quantities in the brain[49–52]. In humans, early evidence of brain insulin synthesis included observation of C-peptide (a by-product of local insulin synthesis) in various cerebral regions[53,54]. Insulin mRNA transcripts have been detected in human post-mortem brain tissue, especially in the hippocampus and hypothalamus, but are present at reduced levels in post-mortem brain tissue from individuals who had AD[55]. Insulin mRNA was also detected by PCR in adult human and mouse brains[56], and chromatin immunoprecipitation assays showed active *Ins2* transcription in mice. *Ins2* mRNA levels were especially high in hippocampus, striatum and thalamus, and intracellular insulin and C-peptide protein immunolabelling was also observed in multiple brain regions, including the hippocampus. Furthermore, the investigators described *de novo* insulin and C-peptide production in mouse primary hippocampal neurons cultured in insulin-free media.

Confirmation of the presence of insulin synthesis in the brain will be crucial, as will be characterization of its localization and regulatory factors. The regional selectivity of insulin synthesis suggests that synthesis and release have a role in the function of local circuits, but this idea is speculative at present.

Effects of insulin in neurons

Insulin has many roles in neurons, and these roles are mediated by signalling through its two major effector pathways: the insulin–IRS–AKT and MAPK pathways[57,58]. Insulin receptors are highly enriched in synapses[59], localizing to both the presynaptic axon terminal[60] and the postsynaptic density compartments[61,62], and have important effects on neurosynaptic functioning[63–66]. Briefly, insulin enhances neurite outgrowth, modulates catecholamine release and uptake, regulates trafficking of ligand-gated ion channels, regulates expression and localization of GABA, *N*-methyl-d-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors and modulates activity-dependent synaptic plasticity (that is, long-term potentiation (LTP) and long-term depression (LTD)) via NMDA receptor signalling and AKT[67]. Furthermore, insulin has a crucial role in the development and maintenance of excitatory synapses[68] and has been shown to promote dendritic spine formation and excitatory synapse development through activation of AKT–mTOR and Ras-related C3 botulinum toxin substrate 1 (RAC1)–cell division control protein 42 homolog (CDC42) pathways[69]. In addition, AKT and GSK3 seem to be crucial for modulation of the balance between LTP and LTD[70]. Finally, by inhibiting apoptosis, insulin promotes neuronal survival[71].

Despite glucose being the major energy source for the brain, the uptake, transport and utilization of glucose in neurons is only influenced by insulin and is not dependent on it[72,73]. The insulin-independent glucose transporter GLUT3 is the major glucose transporter in neurons and is present in very few other cell types in the body. The density and distribution of GLUT3 in axons, dendrites and neuronal soma correlates with local cerebral energy demands[74]. Insulin is not required for GLUT3-mediated glucose transport; instead, NMDA receptor-mediated depolarization stimulates consumption of glucose, which prompts glucose uptake and utilization via GLUT3[73,75].

Although most glucose uptake in neurons occurs via GLUT3[76], insulin-regulated GLUT4 is also co-expressed with GLUT3 in brain regions related to cognitive behaviours — at least in rodents. These regions include the basal forebrain, hippocampus, amygdala and, to lesser degrees, the cerebral cortex and cerebellum[77]. Activation by insulin induces GLUT4 translocation to the neuron cell membrane via an AKT-dependent mechanism[78,79] and is thought to improve glucose flux into neurons during periods of high metabolic demand, such as during learning[80]. Interestingly, GLUT4 is also expressed in the hypothalamus[81], a key area for metabolic control. Deletion of GLUT4 from the CNS in mice results in impaired glucose sensing and tolerance[82], which might be due in part to an absence of GLUT4 in the hypothalamus.

Effects of insulin in glial cells

Astrocytes are the principal homeostatic cells of grey matter and compose 20–40% of all glia in the human brain[83,84]. Astrocytes take up glucose via GLUT1 and can process glucose glycolytically and transport lactate to neurons as an alternative fuel source during hypoglycaemia in a process known as the astrocyte–neuron lactate shuttle[85,86]. The relative contribution of this shuttle as a neuronal fuel source compared with neuronal glucose uptake via glucose transporters is still debated, although it is clear that neurons can use lactate to fuel oxidative phosphorylation and generate ATP during periods of high energy demand[87]. Hyperinsulinaemia is reported to increase peripheral lactate levels, which in turn could affect the net flux of lactate across the BBB and affect energy metabolism within the brain[88]; therefore, the effect of insulin levels on lactate could have implications for brain functioning. Astrocytes bind insulin with high affinity[89] and express IRS1, IRS2 and downstream signalling molecules AKT and MAPK. Functional assays have demonstrated activation of these canonical pathways with insulin or IGF1[90–92]. Interestingly, glial insulin receptors are downregulated in response to chronically high levels of insulin whereas neuronal insulin receptors are not[93]. This finding could have implications for understanding the effects of T2DM on brain function as well as for understanding how insulin resistance can differentially affect various cell types. Finally, astrocytes play a part in inflammatory responses in the brain, and insulin modulates astrocyte inflammatory cytokine secretion in response to inflammatory stimuli in a complex concentration-dependent manner[91].

AKT signalling is important for mediating oligodendrocyte proliferation, survival, differentiation and myelination. The activation of AKT signalling by IGF1 in oligodendrocytes is well established[94] and is known to promote differentiation and axonal ensheathment[95]. Given this cross-signalling between insulin and IGF1, insulin signalling might also contribute to these processes.

Research on human microglial cultures *in vitro* has found that microglia express insulin receptors and IRS1 and that insulin modulates microglial inflammatory responses in a complex manner[91]. Depending on its concentration in culture, insulin can enhance the secretion of certain inflammatory cytokines and inhibit the production of others. In addition, insulin has also demonstrated selective anti-inflammatory and antiviral actions in cultured human primary microglia from HIV-1-infected fetal tissue, as well as in cats infected with feline immunodeficiency virus[96].

Net effects of insulin in the brain: systemic metabolism, cognition and mood

Insulin can provoke a wide variety of effects in cells, and the complexity of insulin's actions is especially evident in the brain owing to the specialized functions of different brain regions, cell types and their networked connections.

Insulin signalling in the CNS regulates metabolic pathways in peripheral tissues such as the liver and adipose tissue, and these effects are thought to be mediated by the actions of insulin in the hypothalamus. In rats, IRS2 is highly expressed in hypothalamus as well as in some other brain areas that regulate feeding, nutrient partitioning and energy balance[97]. Since the 1970s, studies examining intracerebroventricular or direct hypothalamic

administration of insulin in rodents and nonhuman primates have shown that insulin decreases food intake in a dose−dependent manner[98–105], although the robustness of these effects remains controversial[106]. The metabolic effects of brain insulin are also important, including the suppression of hepatic glucose production[107–109], lipolysis in adipose tissue[110,111], hepatic catabolism of branched-chain amino acids[112] and hepatic triglyceride secretion[110], all of which occur independently from plasma insulin levels. Metabolic regulation occurs via modulation of vagal and/or sympathetic efferent fibres, and vagotomy or sympathectomy abrogates suppression of hepatic glucose production or adipose tissue lipolysis, respectively[107,110]. Together, these studies show that the association between T2DM and brain dysfunction might be due to impaired hypothalamic insulin action resulting in disrupted metabolic control and increasing susceptibility to T2DM due to whole-body insulin resistance[113].

In the past few years, studies that utilized intranasal insulin administration have reported substantial effects on cognition and neurophysiology. Acute and chronic intranasal insulin administration improved memory and other cognitive functions in healthy adults with obesity or T2DM[114–123], and neuroimaging studies found that intranasal insulin alters activation of cognitive brain regions and resting-state connectivity between the hippo campal region and the default-mode network[124–126]. Electrophysiology studies, including measurement of event-related potentials[127], direct-current brain potentials[128] and magnetoencephalography[129,130], also detected changes in response to acute intranasal insulin administration in healthy individuals and in people with obesity. On the other hand, in a pioneering study, a well-established hyperinsulinaemic–euglycaemic clamp procedure in elderly individuals with normal cognition or with AD failed to elicit a change in performance on a memory task with insulin compared with saline[131].

Acute glucose administration enhances cognitive functioning[132,133], but chronic hyperglycaemia might negatively affect brain function[134]. However, it remains unclear whether these effects are directly due to the actions of glucose or instead to stimulation of an increased release of insulin or other hormones in response to increased circulating glucose levels. Changes in insulin levels might also affect neuronal glucose uptake and metabolism via GLUT4 translocation in response to insulin–IRS1–AKT signalling in brain regions important for cognitive and emotional function. This process could increase glucose uptake under conditions of high energy demand, as has been observed to occur during hippocampal-dependent learning tasks in rats[135,136].

Given the high density of insulin receptors in limbic cortical and subcortical regions, the fact that insulin also affects mood, reward, motivation and other aspects of psychiatric functioning is to be expected. Indeed, insulin was among the earliest drug treatments for severe psychiatric disorders[137], and an extensive literature exists on the reciprocal relationship between diabetes mellitus and mood[138]. However, the neurobiological role of insulin and insulin signalling in reward-based, motivational and emotional functioning has received limited systematic investigation. In healthy young men, hyperinsulinaemic–euglycaemic clamping decreased hunger and increased wakefulness ratings but had no acute effects on mood[139]. On the other hand, chronic (8-week) intranasal insulin improved multiple aspects of negative affect and memory in obese young men[115].

Brain insulin resistance

Definition

Insulin resistance in T2DM has been defined as “reduced sensitivity in body tissues to the action of insulin”.[140] Similarly, brain insulin resistance can be defined as the failure of brain cells to respond to insulin[141]. Mechanistically, this lack of response could be due to downregulation of insulin receptors, an inability of insulin receptors to bind insulin or faulty activation of the insulin signalling cascade. At the cellular level, this dysfunction might manifest as the impairment of neuroplasticity, receptor regulation or neurotransmitter release in neurons, or the impairment of processes more directly implicated in insulin metabolism, such as neuronal glucose uptake in neurons expressing GLUT4, or homeostatic or inflammatory responses to insulin. Functionally, brain insulin resistance can manifest as an impaired ability to regulate metabolism — in either the brain or periphery — or impaired cognition and mood.

In the following sections, we consider the concept of brain insulin resistance in three settings: T2DM-associated cognitive effects in which systemic insulin resistance might engender brain insulin resistance and brain dysfunction; T2DM-associated neurodegenerative dementias in which systemic insulin resistance is thought to promote neurodegenerative disease pathology; and neurodegenerative disease dementia-associated brain insulin resistance irrespective of T2DM or systemic insulin resistance. As will become evident, we do not yet have a clear understanding of how systemic and brain insulin resistance, cognition and ADRDs relate to one another.

Systemic and brain insulin resistance

Multiple sources of data support a link between T2DM and brain dysfunction — particularly regarding cognitive impairment and ADRDs (BOX 1). Cognitive dysfunction was recognized in patients with diabetes mellitus as early as the 1920s, when Miles and Root described impairments in memory, processing speed and arithmetic abilities[142]. Among early formal studies conducted in the 1980s, Perlmuter *et al.*[143] compared cognition in non-insulin-dependent individuals with T2DM and age-matched nondiabetic controls and reported that more severe deficiencies — including memory deficiencies — were associated with higher haemoglobin A1c levels. Subsequent studies supported these findings and described modest impairments in complex attention, information processing and executive function in individuals with T2DM[18,144–154]. Most studies have been conducted in middle-aged and elderly individuals and found that a higher degree of cognitive impairment is associated with a longer duration of diabetes, poorer glycaemic control and the presence of diabetic complications, as well as common comorbidities such as hypertension and depression. Whether T2DM−associated cognitive impairment or dementia are solely related to cerebro-vascular, ageing or neurodegeneration-related effects remains unclear. Emerging data in young adults and adolescents with T2DM show cognitive and brain structural changes in this burgeoning population, supporting the notion that even early disease processes, and not only cumulative vascular and age-related neurodegeneration, play a part in pathogenesis[155–158].

Neuroimaging studies have revealed differences in brain structure and function in individuals with longstanding T2DM compared with healthy individuals[159,160]. Large-vessel atherosclerosis and stroke, as well as small-vessel ischaemic disease, are more common in individuals with T2DM than in the general population. Cerebral atrophy — especially in cognition-related regions — is also present at a greater frequency in elderly individuals who have insulin resistance and T2DM than in those without either of these conditions. Metabolic imaging with FDG-PET scanning in middle-aged and elderly individuals with insulin resistance (either T2DM or pre-T2DM) who have normal cognition has demonstrated regional cortical hypometabolism in parietal, temporal and frontal regions, which are important for cognition and are frequently implicated in ADRDs[161–163].

Studies have yet to show whether T2DM−associated cognitive impairment and brain neuroimaging findings are a consequence of brain insulin resistance or are due to other factors that co-occur with systemic insulin resistance. Common comorbidities of systemic insulin resistance in T2DM — such as hyperglycaemia, advanced glycation end products, oxidatively damaged proteins and lipids, inflammation, dyslipidaemia, athero sclerosis and microvascular disease, renal failure and hypertension — all have their own complex effects on brain function through a variety of mechanisms independent of insulin signalling. Furthermore, evidence suggests that systemic insulin resistance or high circulating levels of insulin affects the function of the BBB by downregulating endothelial insulin receptors and thus decreasing permeability of the BBB to insulin. This change in permeability is potentially of great importance as it could lead to decreased brain insulin levels and decreased insulin-facilitated neural and glial activity[40]. On the other hand, T2DM can lead to damage of the BBB, which results in increased permeability to a variety of substances[164–166].

Experimental animal models of T2DM have supported the concept that systemic and brain insulin resistance are linked. For instance, genetic models of T2DM (including db/db mice), pharmacologically-induced T2DM models (such as streptozotocin-treated mice) and rodents fed a high-fat diet develop systemic insulin resistance, hyperglycaemia and strong biochemical evidence of brain insulin resistance, as well as memory deficits, synaptic abnormalities (structural, molecular and neurophysiological) and other brain abnormalities[167–170]. Few experimental studies in humans have directly examined whether brain insulin resistance occurs in systemic insulin resistance syndromes such as T2DM. A study that used FDG-PET and hyperinsulinaemic–euglycaemic clamping showed that the global and regional changes (whether increases or decreases) in brain glucose metabolic activity that were evoked by insulin were greater in insulin-sensitive versus insulin-resistant individuals, possibly signifying brain insulin resistance in people with systemic insulin resistance[171]. Other studies have suggested the presence of brain insulin resistance in obesity[130,172]. However, these studies do not clarify whether the brain insulin resistance hypothesized in T2DM is truly brain insulin resistance *per se* or represents inadequate delivery of insulin to the brain — for example, owing to BBB transport deficits due to insulin resistance.

In patients with T2DM who had cognitive dysfunction and reduced interhemispheric connectivity on functional MRI, intranasal administration of insulin normalized connectivity,

improved regional cerebral perfusion and improved cognitive performance[118,125]. This finding suggests that improvements can be achieved either by successful delivery of insulin in the context of impaired BBB transport and normal brain insulin sensitivity or by overcoming brain insulin resistance with larger doses of insulin.

Systemic insulin resistance and ADRDs

A large body of mostly epidemiological evidence suggests that T2DM, obesity and other prediabetic states of insulin resistance are risk factors for AD[3–19,173] and related disorders[11,174–193]. Insulin resistance has been proposed to contribute to neurodegenerative diseases via a number of mechanisms, including promotion of disease-specific pathological lesions and an increase in neuronal vulnerability and neurodegeneration in general[194]. Many T2DM animal model studies have supported this concept that T2DM promotes the development and accumulation of ADRD pathologies, such as amyloid-β plaques, tau phosphorylation and neurofibrillary lesions[195], and α-synuclein lesions[196].

Neuroimaging studies show that T2DM is associated with patterns of brain changes consistent with neurodegenerative dementias, including white matter lesions[197]. Volumetric MRI studies have reported significant correlations between the presence of T2DM, obesity, and/or peripheral insulin resistance and decreased hippocampal volume[198–208], a common although not specific feature of AD. Studies that employ FDG-PET report AD-like regional hypometabolism — for example, in parietotemporal, frontal and cingulate–retrosplenial regions[161,162,209–211]. AD-like differences in regional cerebral blood flow and oxygenation have also been detected with O^{15}-PET[212] and functional MRI[213–220].

By contrast, evidence concerning a relationship between T2DM and molecularly or pathologically defined neurodegenerative diseases in humans is mostly negative. To our knowledge, only one study found that systemic insulin resistance was associated with brain amyloid-β positivity by PET imaging[221]. Others have found no such relationships between measures of longitudinal glucose tolerance and amyloid-β PET or post-mortem AD pathology results[222], no significant differences in PET amyloid-β load between dementia-free elderly people with or without T2DM[163], no differences in amyloid-β PET in a broad sample of diabetic versus nondiabetic elderly individuals with normal cognition, MCI or AD[208], no quantitative difference between individuals with clinical AD dementia with or without diabetes mellitus[223], and a surprisingly low frequency of amyloid-β-positive PET scans in patients with diabetes mellitus who had been clinically diagnosed with AD dementia[224].

The same group that reported systemic insulin resistance associated with PET amyloid-β load also found modest and variable associations between insulin resistance and CSF measures of AD pathology, including the phosphorylated tau 181 (phospho-tau_{181}):amyloid-β_{42} ratio and some (but not all) amyloid-β species[221].

However, others have found increased total tau and phospho-tau levels in patients with T2DM but no association between T2DM and amyloid PET findings or CSF levels of amyloid-β[208]. Starks and colleagues found no direct association between systemic insulin resistance and CSF amyloid-β, total tau or phospho-tau levels, although they did find a

positive association with measures of tau (but not amyloid-β) in individuals positive for apolipoprotein E (APOE) ε4[225].

The relationship between T2DM and the degree of AD pathology in the brain at autopsy is almost uniformly negative[185,190,226–231]. Studies that considered the *APOE* genotype in patients with T2DM reported that the extent of AD pathology was higher in those with T2DM who carried the *APOE* ε4 allele than those who did not[190,232], but the importance of the *APOE* ε4 allele with regards to T2DM itself was not clear. In another study, daily average blood glucose level was not found to be associated with the presence of amyloid-β plaques, paired helical filament tau tangles, Lewy bodies or vascular lesions but was associated with hippocampal sclerosis[233]. To our knowledge, neuropathological studies examining the association between T2DM and other neurodegenerative disease pathologies have not been conducted, although post-mortem neuropathology studies have established an association between T2DM and post-mortem assessments of cerebrovascular disease. Brains from individuals who had T2DM have more arteriolosclerosis with ischaemic rarefaction of white matter, large-vessel atherosclerosis, lacunar infarcts, thromboembolic stroke, haemorrhagic stroke and aneurysmal subarachnoid infarcts than do those from individuals who were free from diabetes[185,190,229–231,234–237].

As most of the aforementioned studies were cross-sectional and performed after the onset of clinical AD symptoms, they largely fail to account for the time course of disease progression in AD. Amyloid-β deposition in the brains of patients with AD begins 10–20 years before the manifestation of clinical symptoms[238]. Consequently, aspects of T2DM such as hyperglycaemia, hyperinsulinaemia or insulin resistance might affect the rate of AD pathology-associated production, clearance and accumulation during the preclinical stage[239,240], but these aspects would be missed in studies focused on patients with symptomatic AD. With the advent of new neuroimaging technologies for both amyloid-β and tau, additional longitudinal studies should focus on individuals who are asymptomatic so as to facilitate the investigation of features of T2DM that might alter the course of ADRDs.

Shared genetic risk factors also might play a part in any associations between T2DM and ADRDs, although the common (that is, sporadic) forms of T2DM and AD both have weak hereditary contributions to risk. Two reports described *APOE* ε4 as an independent risk factor for T2DM; however, these studies had small sample sizes and focused on the effects of *APOE* on T2DM or cardiovascular comorbidity[241,242]. Other studies investigated only how *APOE* genotype modifies the relationship between T2DM and vascular disease and found that *APOE* ε4 increases risk of largevessel and small-vessel disease. T2DM and AD have also been associ ated with polymorphisms in genes that confer small risk effects[243–247]. Although some common pathways are found in gene lists for T2DM and AD (for example, metabolism, immunity and intracellular trafficking), only one gene, *SORCS1*, has been linked to both diseases[248–250]. However, the basic molecular and cellular pathogenic mechanisms underlying the susceptibility conferred by *SORCS1* to AD and T2DM remain poorly understood.

Brain insulin resistance in ADRD, irrespective of T2DM

Advanced age is associated with systemic insulin resistance, but the degree to which this resistance occurs in the brain[251–254], and the relationship of the brain to body insulin resistance in ageing and ADRDs, is not established. Decreased insulin concentrations and insulin receptor binding were reported in the cortex of elderly individuals without dementia (68–93 years old) compared with young and middle-aged adults (21–62 years old) without AD[54]. Insulin receptor binding was also reduced in elderly individuals with AD (67–91 years old) compared with the young and middle-aged adults, but insulin receptor binding was higher, curiously, in individuals in the elderly AD group compared with that in elderly controls. By contrast, subsequent studies of insulin receptor expression and binding in humans have principally compared individuals who have AD with age-matched controls and suggest decreased expression of insulin receptor mRNA and protein and decreased insulin receptor binding in individuals with AD[55,255] that correlates with pathological severity[255]. However, others have reported unchanged levels of insulin receptor protein associated with AD[75,256].

A substantial body of literature describes evidence of insulin signalling pathway abnormalities in postmortem brain tissue from individuals who had AD. Hoyer first proposed the concept of brain insulin resistance in AD over 25 years ago as one explanation for the glucose hypometabolism observed in AD[257,258]. In 2005, de la Monte and colleagues reported reductions in the mRNA and protein expression levels of insulin, insulin receptor, IGF1 and IGF2, and reduced total IRS1 mRNA expression, reduced protein indicators of downstream insulin signalling activity (including p85-associated IRS1, phosphorylated AKT (pAKT) and phosphorylated GSK3β), reduced tau mRNA and increased amyloid precursor protein mRNA in post-mortem AD brain[55]. Furthermore, they found associations between these effects and a number of important neuropathological features of AD, including Braak stage, astroglial and microglial markers and choline acetyl transferase expression[255]. Together, these findings were interpreted as showing impaired insulin and IGF1 signalling in AD, akin to that detected in T2DM. Similar findings were subsequently described in Lewy body disease[259].

Although some findings of these early studies remain controversial, human post-mortem studies of AD have consistently described major abnormalities in the expression and/or activation states of insulin signalling molecules[75,256,260–269]. In an especially comprehensive study of human post-mortem hippocampal tissues from nondiabetic elderly adults with and without AD, Talbot and colleagues described abnormal activation states of many key components and regulators of the insulin receptor–IRS1–AKT–mTOR and GSK3 pathways. The study used a novel *ex vivo* insulin signalling stimulation paradigm that experimentally demonstrated insulin resistance in AD[75]; stimulation with physiological doses of insulin in hippocampal tissue from normal postmortem brain tissue robustly activated insulin signalling as measured by increased phosphorylation of insulin receptor subunit β, IRS1, AKT and GSK3α and GSK3β, whereas tissue from AD brains (matched for age, sex and post-mortem interval) had dramatically reduced insulin-stimulated activation throughout the pathway. In two independent samples of post-mortem brains from individuals who had AD or MCI, substantial abnormalities were described in the basal phosphorylation states of IRS1

and its many serine kinases[75,266]. These abnormalities correlated positively with measures of amyloid-β and tau lesions and negatively with global cognition and memory scores. Interestingly, the associations remained even after controlling for amyloid-β and tau lesions, suggesting that insulin resistance contributed independently from cognitive impairment (BOX 2).

Brain insulin resistance might also be a feature of other neurodegenerative diseases. Insulin receptor mRNA and protein expression were reported to be decreased in the substantia nigra and/or basal ganglia in Parkinson disease, as were expression levels of AKT and pAKT[270–272]. One study that focused on serine phosphorylated IRS1 (pS-IRS1) as a nodal marker of insulin signalling pathway inhibition replicated earlier findings demonstrating highly abnormal pS-IRS1 expression in AD but also showed increased pS-IRS1 in tauopathies (Pick disease, corticobasal degeneration and progressive supranuclear palsy) but not in synucleinopathies (Parkinson disease, dementia with Lewy bodies and multiple system atrophy) or TAR DNA-binding protein 43 (TDP-43) proteino pathies (frontotemporal lobar degeneration with TDP-43, and amyotrophic lateral sclerosis)[267].

Prompted by many of these findings, investigators have proposed that increasing the concentrations of brain insulin in people with AD might have preventive, disease-modifying or symptomatic therapeutic effects. As noted previously, intranasal insulin administration enhances memory functions in healthy individuals and in those with insulin resistance[114–123,273]. This finding was also observed in patients with AD or MCI, but only in those who did not carry an *APOE* ε4 allele[119,122]. A subsequent pilot trial lasting 4 months and including more than 100 patients with AD and MCI found that individuals receiving daily intranasal insulin had moderately improved cognitive and functional capacities and improved FDG-PET metabolism[120]. Improvements persisted at least 2 months after discontinuation of treatment, suggesting the presence of a disease-modifying effect.

Aside from treatment with insulin itself, insulin-sensitizing medicines commonly used in T2DM have attracted growing interest as potential therapies for brain insulin resistance in ADRD[274]. For instance, investigators have begun testing of metformin, the most commonly prescribed drug for T2DM, in nondiabetic individuals with MCI or early dementia due to AD, with some signs of benefit[275,276]. In addition, thiazolidinedione-based nuclear peroxisome proliferator-activated receptor-γ (PPARγ) agonists, which were originally developed as insulin sensitizers for T2DM, have shown numerous beneficial neural effects in animal models of neurodegenerative diseases[277]. However, large clinical trials of the PPARγ agonist rosiglitazone failed to show primary end point benefit in AD[278], and results are pending for a definitive clinical trial of another such agonist, pioglita-zone (NCT01931566), which has shown promising early results and better BBB penetration than rosiglitazone. Glucagon-like peptide 1 (GLP-1) - targeting drugs are another category of insulin sensitizers showing promise in AD in preclinical and early clinical trial studies[279]. However, whether these approaches improve ADRDs via their insulin-sensitizing effects on brain cells or via their other complex signalling mechanisms of action is uncertain.

Conclusion and call to action

We have reviewed a large and rapidly growing literature on insulin signalling in the brain during normal adulthood and ageing and in individuals with T2DM and ADRDs. Cellular insulin resistance, whether in the brain or other tissues of the body, is defined as an impaired molecular signalling response to insulin. At the organism level, insulin resistance can be defined by the impaired ability of insulin to regulate physiology. Functionally, brain insulin resistance can manifest as impaired central regulation of nutrient partitioning, cognitive and mood dysfunction, and brain-specific neuropathology and neurodegeneration. A relationship seems to exist between systemic insulin resistance in T2DM and/or prediabetes and brain insulin resistance, but it remains poorly defined, as does the relationship between systemic insulin resistance and ADRDs. T2DM and AD are both associated with brain insulin resistance and brain dysfunction; however, T2DM might not be associated with AD in any meaningful manner, at least as pathologically defined. At present, we are left with many fundamental questions, the answers to which would help to resolve this essential conundrum (BOX 3).

Globally, the epidemics of T2DM and AD are growing and have enormous costs — both in terms of human suffering and economic burden. Urgent action is needed to accelerate the empiric and rational development of preventive, disease-modifying and symptomatic treatments based on thoughtfully designed mechanistic studies and improved understanding of these diseases. Much is known about the biology of each of these diseases separately, and recognition of their pathophysiological intersection is growing. Whether T2DM and AD are parallel phenomena arising from similar factors rooted in insulin resistance and metabolic dysfunction or are synergistic diseases somehow linked in a vicious pathophysiological cycle must be studied. Increasing interdisciplinary knowledge of commonalities and differences in insulin resistance in the body and brain will yield dividends for our understanding and management of both T2DM and AD.

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Key points

- The molecular signalling pathways through which insulin exerts its actions in the body also mediate its roles in synaptic neurotransmission, neuronal and glial metabolism, and the neuroinflammatory response in the brain
- The actions of insulin in the brains of healthy individuals include central modulation of body metabolism and enhancement or regulation of memory and other cognitive and emotional functions
- Insulin resistance is a core feature of type 2 diabetes mellitus (T2DM) and contributes not only to the hyperglycaemia that defines diabetes mellitus but also to the hyperlipidaemia, inflammation, oxidative stress and atherosclerosis that accompany it
- T2DM substantially increases risk of not only cerebrovascular disease and stroke but also neurodegenerative dementias of late life, especially Alzheimer disease (AD)
- Brain insulin resistance can be defined as the failure of brain cells to respond to insulin as they normally would, resulting in impairments in synaptic, metabolic and immune response functions
- T2DM is associated with brain insulin resistance, and studies suggest that brain insulin resistance is a feature of AD; however, whether the two conditions are mechanistically linked or represent unrelated occurrences in ageing is unclear

Box 1

Clinical links between T2DM and ADRDs

Research has uncovered a number of clinical features in individuals with type 2 diabetes mellitus that support a relationship (or lack thereof) with Alzheimer disease and related disorders. Major findings include

- Modest cognitive deficits, especially in
  - Attention
  - Information processing
  - Executive function
  - Memory
- Mood disorders, especially depression
- Large-vessel atherosclerotic and small-vessel ischaemic disease
- Cerebral atrophy
- Hypometabolism in parietal, temporal and frontal cortices
- Impaired insulin-mediated activation of metabolic and electroencephalographic activity
- Increased risk of progressive neurodegenerative dementias
- Negative (mostly) molecular neuroimaging and cerebrospinal fluid biomarker findings for abnormal levels of amyloid-β and tau
- Negative neuropathological findings of amyloid-β plaques or tau tangles

Box 2

Brain insulin resistance in ADRDs

- Increasing age is associated with decreasing cortical insulin concentration and receptor binding in older adults without dementia
- Brain tissue from those with Alzheimer disease (AD) shows major abnormalities in insulin signalling, including
  - Decreased insulin, insulin receptor and insulin receptor substrate 1 (IRS1) mRNA and/or protein expression levels
  - Decreased activation of insulin pathway molecules (for example, IRS1 and AKT) with *ex vivo* stimulation
  - Increased basal phosphorylation levels of multiple insulin–IRS1–AKT pathway molecules
  - Positive correlation between phosphorylated IRS1 and other pathway molecules and AD pathology
- Intranasal insulin administration improves cognitive functioning in humans with AD or mild cognitive impairment and improves measures of insulin signalling, amyloid-β and cognitive behaviours in AD model mice
- Brain insulin resistance might be a feature of other neurodegenerative diseases
  - Insulin receptor expression is decreased and AKT signalling is abnormal in the substantia nigra in Parkinson disease
  - Abnormal phosphorylated IRS1 expression is observed in tauopathies but is not seen in synucleinopathies or TDP-43 proteinopathies

Box 3

Questions regarding the mechanistic relationship between T2DM and ADRDs

- Is insulin produced in the brain or not? If so, where, how much and by what means?
- Does type 2 diabetes mellitus (T2DM) affect the blood–brain barrier? Are insulin concentrations increased or decreased in the brain and cerebrospinal fluid in T2DM and in Alzheimer disease (AD) and related disorders (ADRDs)?
- How does insulin and insulin resistance affect glial cell function?
- What are the mechanisms in T2DM that lead to brain insulin resistance and cognitive impairment? Do hyperglycaemia, hyperinsulinaemia, hypoinsulinaemia, dyslipidaemia, hypertension, renal failure, microvascular disease, adipokine or incretin effects, oxidative stress, advanced glycation end products, inflammation or other associated causes and consequences of T2DM play a part?
- How does T2DM increase the risk of AD and possibly other neurodegenerative dementias? Does it promote the molecular neuropathology of these diseases? Does it weaken the neural systems or neuroplastic resilience factors so that injurious effects of plaques, tangles or other pathologies are magnified, with greater clinical expression per unit of pathology? How do we improve the design of studies aimed at a preclinical population to capture the interaction between T2DM and ADRD pathologies?
- How important is the brain insulin resistance observed in AD to the neurodegenerative process? Is it a consequence, a cause or part of a vicious cycle with amyloid-β and tau pathologies?
- Does AD impair brain insulin action with regards to systemic metabolic control, and would this effect in turn increase susceptibility to T2DM?
- Which metabolic pathways regulated by brain insulin (for example, lipolysis in adipose tissue, hepatic glucose production or branched-chain amino acid metabolism) are disrupted in AD?
- Might the insidious and protracted accumulation of neurodegeneration in the brain (including the hypothalamus) in AD alter the central regulation of body energy metabolism and even promote systemic insulin resistance and T2DM?

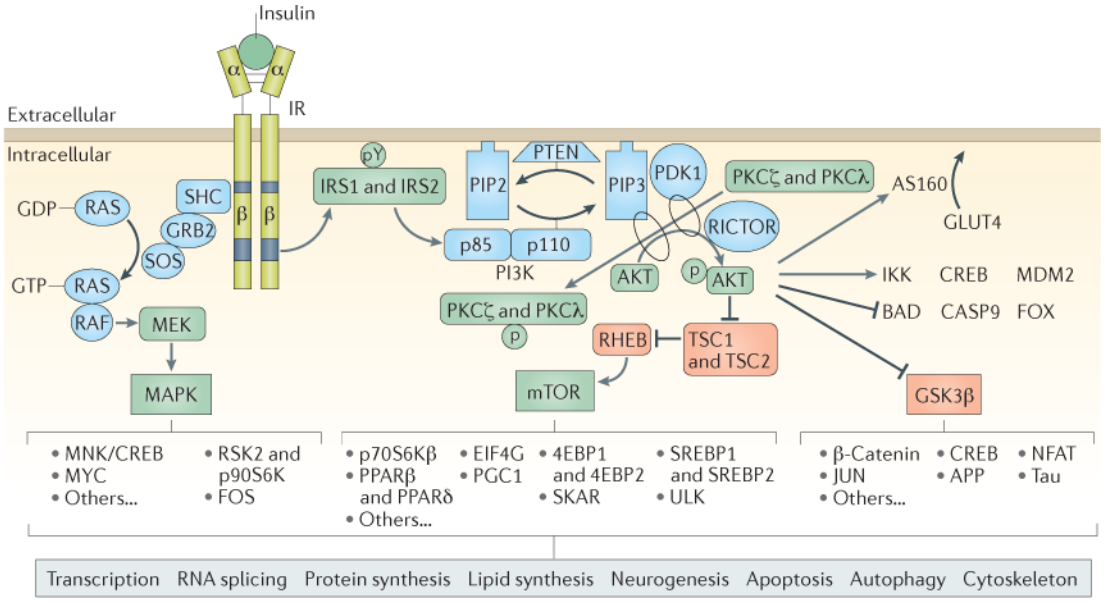

Figure 1. Canonical insulin signalling pathways

Insulin binds extracellular α-subunits of the insulin receptor (IR), leading to dimerization and autophosphorylation of β-subunits and activation of its kinase activity. The IR phosphorylates select tyrosine residues (pY) on insulin receptor substrate 1 (IRS1) and IRS2, leading to exposure of binding sites for signalling partners. IRS1 and IRS2 recruit and activate the phosphoinositide 3-kinase (PI3K) complex, which then phosphorylates and activates AKT, the major node of the insulin signalling cascade, as well as protein kinase Cζ (PKCζ) and PKCλ. Activated AKT has many downstream effects: of greatest relevance to systemic glucose control, AKT phosphorylates AKT substrate of 160 kDa (AS160; also known as TBC1D4), which controls the translocation of glucose transporter type 4 (GLUT4) to the cell membrane for uptake of glucose into muscle, adipose and some neurons. AKT-mediated activation of mTOR and the downstream targets of mTOR serves to regulate protein and lipid synthesis and many aspects of cell metabolism, growth, survival and autophagy. Phosphorylation of glycogen synthase kinase 3β (GSK3β) by AKT inhibits the constitutive activity of this key kinase. GSK3β has many protein substrates, such as glycogen synthase, β-catenin, microtubule-associated proteins (including tau), intermediate filaments, cAMP-responsive element-binding protein (CREB) and others. Through these diverse proteins, insulin and GSK3β signalling play important parts in the regulation of cellular proliferation, migration, glucose regulation, apoptosis and neuroplasticity. AKT kinase activity also directly activates proteins such as inhibitor of nuclear factor-κB kinase (IKK), CREB and E3 ubiquitin-protein ligase Mdm2 (MDM2) to regulate transcription, cytokine production and cell survival, and it directly inhibits selected proteins, including regulators of apoptosis (Bcl2-associated agonist of cell death (BAD) and caspase 9 (CASP9)) and Forkhead box protein (FOX) transcription factors. Independent of IRS1 and IRS2 and AKT, IR kinase activity initiates the activation of the mitogen-activated protein kinase (MAPK) pathway, which is especially important for regulating the transcription of CREB, Myc proto-oncogene protein (MYC) and ribosomal protein S6 kinase 2 (RSK2; also known as S6Kα3), affecting cell proliferation, differentiation, innate and adaptive immune

function and neuroplasticity. Importantly, AKT, GSK3β, mTOR and MAPK themselves provide feedback autoregulation of IRS1 and IRS2, inhibiting their activity through site-specific serine phosphorylation. 4EBP, eukaryotic translation initiation factor 4E binding protein; APP, amyloid precursor protein; EIF4G, eukaryotic translation initiation factor 4γ; FOS, proto-oncogene c-Fos; GRB2, growth factor receptor-bound protein 2; JUN, transcription factor AP-1; MEK, MAPK/ERK kinase (also known as MAPKK); MNK, MAP kinase signal-interacting kinase (also known as MKNK); NFAT, nuclear factor of activated T cells; p70S6Kβ, p70 ribosomal S6 kinase β (also known as S6Kβ2); p90S6K, 90 kDa ribosomal protein S6 kinase 1 (also known as S6Kα1); PDK1, 3-phophoinositide-dependent protein kinase 1; PGC1, PPARγ coactivator 1; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; PPAR, peroxisome proliferator-activated receptor; RICTOR, rapamycin-insensitive companion of mTOR; SHC, SHC-transforming protein; SKAR, S6K1 Aly/REF-like target (also known as POLDIP3); SOS, son of sevenless homologue; SREBP, sterol regulatory element-binding protein; TSC1, hamartin; TSC2, tuberin.

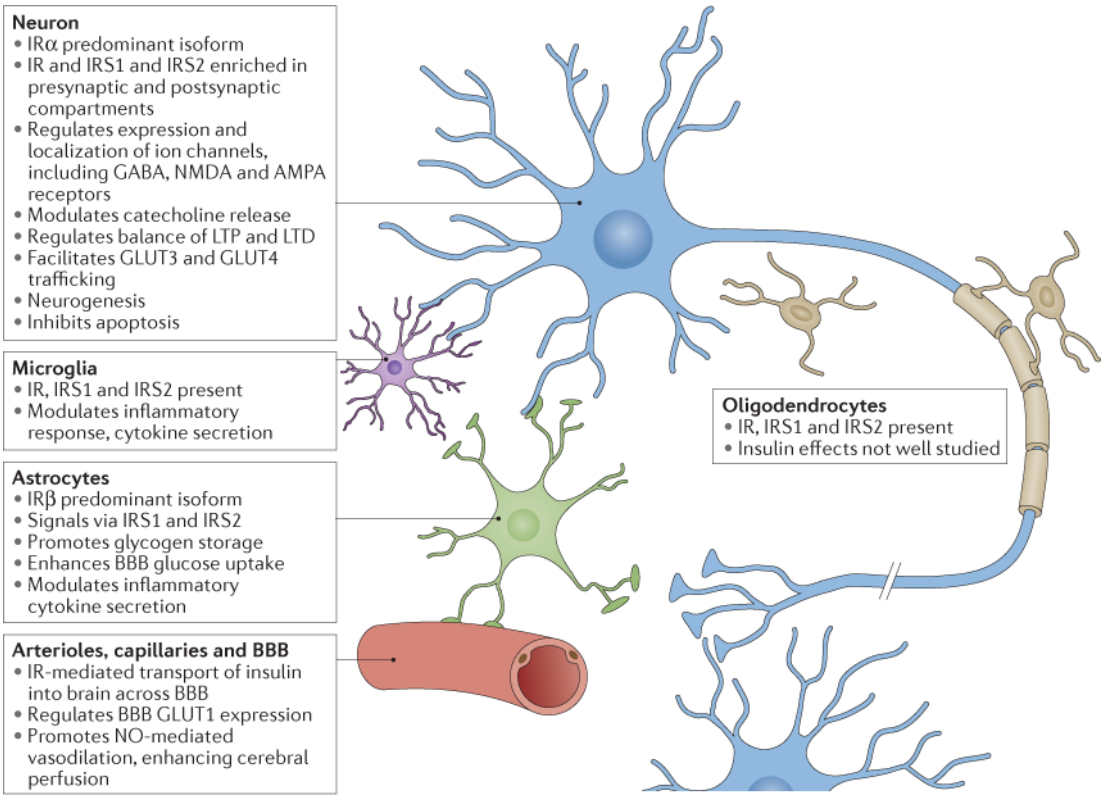

Figure 2. Insulin effects in major cell types of the brain

Main characteristics of insulin signalling in neurons, astrocytes, microglia and the vascular system. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; BBB, blood–brain barrier; GLUT, glucose transporter type protein; IR, insulin receptor; IRS, insulin receptor substrate; LTD, long-term depression; LTP, long-term potentiation; NMDA, *N*-methyl-d-aspartate; NO, nitric oxide.