Insulin and neurodegenerative disease: shared and specific mechanisms

Suzanne Craft and G Stennis Watson

Insulin has functions in the brain and dysregulation of these functions may contribute to the expression of late-life neurodegenerative disease. We provide a brief summary of research on the influence of insulin on normal brain function. We then review evidence that perturbation of this role may contribute to the symptoms and pathogenesis of various neurodegenerative disorders, such as Alzheimer's disease, vascular dementia, Parkinson's disease, and Huntington's disease. We conclude by considering whether insulin dysregulation contributes to neurodegenerative disorders through disease-specific or general mechanisms.

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Neurons share more similarities with the insulin-producing pancreatic islet cell than with any other cell type. The root of this similarity may lie in the islet's evolution from an ancestral insulin-producing neuron.[1] Their close association becomes less surprising as we learn more about insulin's involvement in functions far removed from its role in the mediation of glucose uptake. Its importance in the regulation of ageing has been established by the noticeable increases in longevity experienced by animals in which the adipose insulin receptor has been genetically eliminated, or in which the insulin-related daf genes have been mutated. Although the precise mechanisms through which lifespan is changed in these animals remain unknown, lowering of peripheral insulin concentrations and overall improvement of insulin efficiency are likely candidates.[2] Recently, the role of insulin in brain ageing has received increasing attention, along with the possibility that dysregulation of its functions may contribute to neurodegenerative disease in late life. In this review, we focus on how insulin dysregulation has been implicated in the pathophysiology and clinical symptoms of Alzheimer's disease (AD), vascular dementia, Parkinson's disease (PD), and Huntington's disease (HD). We will begin with a brief description of the role of insulin in normal brain function to provide a context for readers unfamiliar with this new and growing area of research.

Insulin and the brain

As recently as 10 years ago, the brain was described as "an insulin insensitive organ" in medical textbooks. Evidence for the presence of insulin and its receptors in the CNS has challenged that notion.[3,4] Insulin is readily transported into the CNS across the blood–brain barrier by a saturable, insulin receptor-mediated transport process.[5–8] The raising of the peripheral insulin concentration acutely increases the concentration in the brain and CSF, whereas prolonged peripheral hyperinsulinaemia downregulates blood–brain barrier insulin receptors and reduces insulin transport into the brain.[9] Insulin receptors are located in synapses on both astrocytes and neurons.[10] Although insulin and insulin receptors are abundant in the brain, they are selectively distributed. In rodents, insulin binding is highest in the olfactory bulb, cerebral cortex, hippocampus, hypothalamus, amygdala, and septum.[8,11–13] Insulin receptors are also concentrated in the substantia nigra, basal ganglia, and frontal cortex.[3,13,14]

An intriguing question concerns the presence and role of brain-derived insulin in mature human beings. Neuronal insulin synthesis has been shown in animals.[1,15,16] However, several questions must be resolved before we can conclude that brain-derived insulin makes substantive functional contributions in adult human beings.

The localisation of insulin receptors in the hippocampus and medial temporal cortex in rats is consistent with evidence that insulin influences memory.[17] In rats, acute intracerebroventricular insulin enhanced memory on a passive-avoidance task.[18] In human beings, acute intravenous insulin enhanced story recall;[19] acute rises in the concentration of insulin in the plasma caused the concentration of insulin in the brain to rise and may thereby facilitate memory. Insulin given intranasally has been shown in animal models to be transported into hypothalamus and hippocampus, without appreciably affecting blood insulin or glucose concentrations, and is associated with increased memory performance in human beings.[20] Conversely, learning may also influence insulin-receptor expression or function. For example, in rats trained on a spatial memory task, the amount of insulin receptor messenger RNA in the dentate gyrus and hippocampal CA1 field was high. This training also increased the concentration of insulin receptor protein in the crude hippocampal synaptic membrane fraction.[21] Thus, learning is accompanied by changes in insulin signalling molecules in the hippocampus. Collectively, these studies suggest that insulin may contribute to normal memory function.

Paradoxically, other findings suggest that chronic hyperinsulinaemia and insulin resistance, or reduced insulin

Both authors are at the Geriatric Research, Education, and Clinical Center, Veterans Affairs Puget Sound Medical Center, Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, USA.

Correspondence: Dr Suzanne Craft, GRECC S-182, VAPSHCS, 1660 South Columbian Way, Seattle, Washington 98108, USA. Tel +1 206 277 1156; fax +1 206 764 2569; email scraft@u.washington.edu

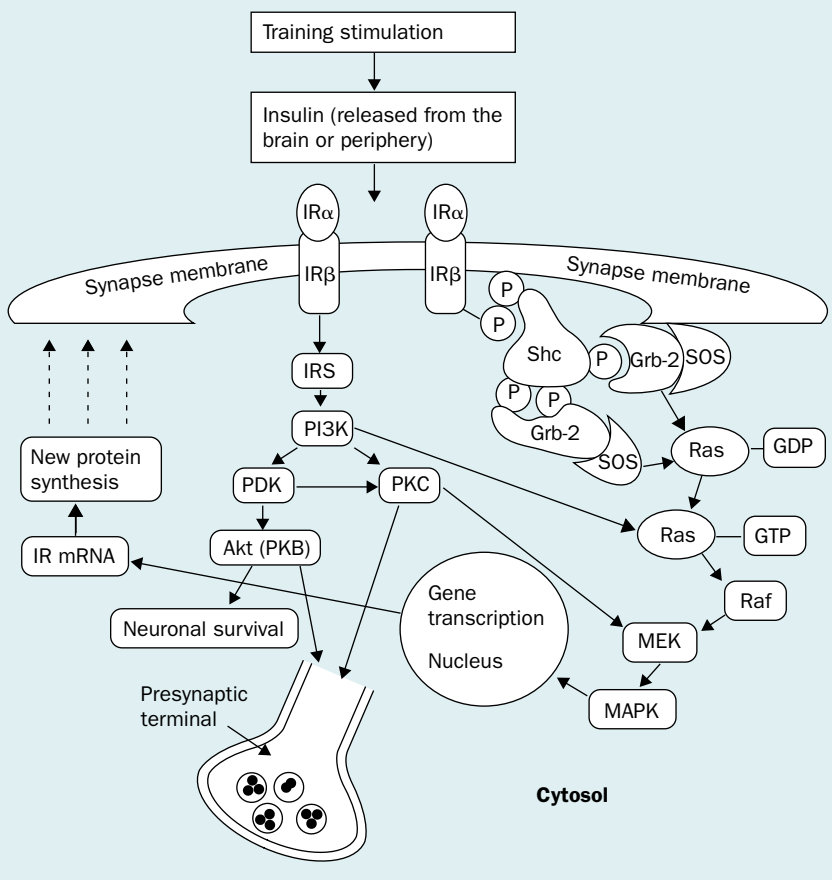

Figure 1. Schematic representation of insulin-receptor mediated signalling pathways involved in learning and long-term memory formation. IR=insulin receptor; IRS=insulin receptor substrate; PI3K=phosphatidylinositol 3 kinase; PKC=protein kinase C; PDK=phosphoinositide-dependent kinase. Reproduced with permission from Elsevier.[42]

effectiveness, may exert a negative influence on memory. For example, type 2 diabetes mellitus has been associated with impairment of both operant learning and classic conditioning in animals[22,23] and with verbal and visual memory decrements in human beings.[24–28] Furthermore, impaired verbal memory has been reported in individuals with hyperinsulinaemia but not chronic hyperglycaemia, as shown by normal concentrations of glycosylated haemoglobin.[29] Taken together, these findings are consistent with acute and chronic hyperinsulinaemia having opposing effects on the neural substrates of memory.

There are several mechanisms through which insulin may affect memory. Although insulin does not seem to influence basal cerebral glucose metabolism or transport of glucose into the brain, evidence suggests regionally specific effects on glucose metabolism. For example, although hyperinsulinaemia does not affect whole-brain glucose use in rodents, it does affect glucose use in specific regions.[30–32] When rats were given peripheral insulin infusion for 4 days, glucose metabolism changed in the anterior hypothalamus, basolateral amygdala, medial geniculate, suprachiasmic nucleus, supramammillary bodies, and locus coeruleus.[30] Several PET studies in human beings found no acute insulin effects on glucose transport into the brain.[33,34] However, Bingham and colleagues[35] found an increase in cerebral glucose metabolism at low insulin concentrations that was most apparent in cortex. The basis for regional insulin effects on glucose metabolism is likely to be the distribution of various glucose transporter isoforms. Insulin-sensitive GLUT4 and GLUT8 glucose transporters are selectively distributed in the brain. In rats, GLUT4 transporters are expressed in the cerebellum, sensorimotor cortex, hippocampus, pituitary, and hypothalamus.[36–39] Similarly, GLUT8 transporters, also known as GLUTX1 transporters, have been found in the hippocampus and hypothalamus.[40,41] The overlapping distributions of insulin, insulin receptors, and insulin-sensitive glucose transporters are consistent with the possibility of insulin-stimulated glucose uptake in specific brain regions, such as the hippocampus and hypothalamus.[3,36]

Other insulin-related mechanisms, not directly related to modulation of glucose uptake, have been implicated in normal hippocampal function. Zhao and Alkon[42] provide an extensive review of the molecular features of insulin's role in learning and memory (figure 1). For example, insulin may modulate long-term potentiation, a molecular model of learning. Long-term potentiation can be induced by NMDA receptor activation, thus increasing neuronal Ca^{2+} influx. A high intracellular concentration of Ca^{2+} presumably activates α-calcium-calmodulin-dependent-kinase II and other Ca^{2+}-dependent enzymes, which results in stronger synaptic associations between neurons. Insulin may influence several constituents of this cascade, such as the cell membrane expression of NMDA receptors,[43] which affect the likelihood of long-term potentiation. Insulin also modulates CNS concentrations of neurotransmitters, such as acetylcholine and norepinephrine, which influence cognitive function.[44,45]

Thus, insulin affects many mechanisms related to neuronal activity and cognitive function supported by such activity. Additionally, insulin seems to have a role in the regulation of ageing-related processes. The stage is now set to consider how insulin dysregulation may affect brain function in ageing. As will be evident, most work to date has focused on the link between insulin and AD. The case is building, however, for an association with other neurodegenerative disorders.

Alzheimer's disease

Early observations that many patients with AD had impaired glucose tolerance were typically attributed to low physical activity or dietary differences. Specifically, a substantial

proportion of adults with AD had high insulin concentrations in response to glucose challenge and reduced insulin-mediated glucose uptake. This pattern is characteristic of insulin resistance, in which more insulin is required to accomplish some of its physiological functions. Further inquiry established that this pattern characterised patients at very early stages of disease, who did not differ from healthy similarly-aged adults on indices of physical inactivity or dietary composition.[46] An interesting pattern was observed, in that high insulin concentrations and reduced insulin-mediated glucose uptake characterised patients with AD without the apolipoprotein E ϵ4 allele (*APOE* ϵ4; a well-established genetic risk factor), and suggested that hyperinsulinaemia and insulin resistance may be a new class of risk factors for this group of patients, who comprise half of all adults with late onset AD.

Peripheral insulin abnormalities

The association of AD and several syndromes related to peripheral hyperinsulinaemia and insulin resistance, such as type-2 diabetes mellitus, has been largely borne out in epidemiological work, although some inconsistency has been noted. A clear association has been shown between dementia and diabetes. However, whether an independent association exists between diabetes and either AD or vascular dementia is more controversial, and there are many methodological challenges to the assessment of this question. The diagnosis of vascular dementia is potentially problematic in large samples, particularly those in which neuroimaging is not routinely done, and diagnostic criteria can result in very different prevalence estimations for vascular dementia.[47] Additionally, recent neuropathological studies suggest that many adults over the age of 80 diagnosed with vascular dementia actually have neuropathological changes consistent with AD.[48] Furthermore, the issue of comorbid dementias is not easily resolved in such studies. There are similar issues in the diagnosis of type-2 diabetes mellitus. Most large-scale studies rely on self-report or treatment records for the diagnosis of diabetes. However, this method may underestimate by half the prevalence of type-2 diabetes mellitus and exclude its predromal state of impaired glucose tolerance, which is also characterised by hyperinsulinaemia and insulin resistance.[49] Furthermore, little consideration is given to the clinical heterogeneity of diabetes, which is defined solely on the basis of hyperglycaemia. As such, the construct of type-2 diabetes mellitus may be analogous to the non-specific term "dementia", in that the clinical symptoms can be have several causes.

With these caveats in mind, reviews of longitudinal studies have generally found that diabetes is associated with an increased risk for impaired cognition or dementia.[24,50–54] Several studies have reported a high risk of AD in patients with type-2 diabetes mellitus that, in some studies, was high with insulin treatment or in one sex.[51–55] In a longitudinal study of Japanese-American men there was no relation of a 15 year or 25 year history of diabetes to AD,[56] possibly because diabetes was assessed at baseline with no further ascertainment during the long follow-up period. In support of this possibility, a later study with the same sample showed a high risk of AD in patients diagnosed with type-2 diabetes mellitus.[57]

Special attention may be warranted for population-based studies that directly assessed diabetes, hyperinsulinaemia, and insulin resistance with oral glucose tolerance testing and used neuroimaging to facilitate differential diagnosis of AD and vascular dementia. Most methodologically sound studies have shown an increased risk of both AD and vascular dementia associated with diabetes and insulin resistance. Two prospective, population-based cohort studies reported such an association.[54,57] In addition, one group of researchers found that the co-occurrence of diabetes and *APOE* ϵ4 synergistically increased the risk of AD.[57] In a cross-sectional population-based study, an increase in the plasma concentration of insulin while fasting was associated with AD both in people with diabetes and in those without, which suggests that insulin resistance independent of diabetes may increase disease risk.[58] A recent study in which 682 people without dementia were followed-up for 3200 person years had similar results.[59] An increased hazard ratio was observed for cases in the highest insulin quartile. This association was strengthened when cases without diabetes were considered. Furthermore, higher insulin concentrations were related to a faster decline in memory-related scores.

How insulin abnormalities may contribute to the symptoms and pathogenesis of AD have been examined in various experimental model systems. As described previously, a role for insulin has been established in molecular and neurophysiological features of memory processing.[42] The giving of insulin while maintaining euglycaemia improves memory in both healthy adults and people with AD.[19,60] Interestingly, the dose at which memory improves varies according to diagnosis and *APOE* genotype. Adults with AD without the *APOE* ϵ4 allele need higher doses of insulin to manifest memory facilitation than normal adults or patients with AD with the ϵ4 allele, which is consistent with the theory of insulin resistance.[61] Infusion of insulin also lowered plasma concentrations of the amyloid precursor protein (APP; from which amyloid-β peptide [Aβ] is generated) in healthy people and patients with AD; higher insulin concentrations were needed for the *APOE* ϵ4 negative AD group.[61]

Insulin in the CNS

The studies discussed so far were of peripheral glucose metabolism. Other investigations have focused on markers of insulin metabolism in the brain or CSF. Hoyer[62] was the first to suggest that desensitisation of the neuronal insulin receptor had a role in AD; he proposed that low concentrations of insulin in the CNS, accompanied by reduced receptor numbers and signalling events in AD, leads to a reduction in acetylcholine and a corresponding decrease in cerebral blood flow. These abnormalities result in chronic and increasing deficits in brain oxidative metabolism. Increased acidosis in intracellular compartments such as the Golgi apparatus and the endoplasmic reticulum may interfere with processing of proteins such as APP in these compartments, creating a favourable environment for the generation of Aβ. In support of his theory, Frolich and co-workers[63] found a reduction in the number of insulin receptors and markers of tyrosine kinase activity in AD. CSF insulin concentrations have also been reported to be low in AD, which presumably corresponds

to a reduction in the concentration of insulin in the brain.[64] However, results of another study of Japanese patients with AD did not show reduced CSF concentrations of insulin.[65]

Insulin, Aβ, and neuropathology

Clinical and neuropathological evidence thus suggests a defect in insulin metabolism in some patients with AD that may be linked to *APOE* genotype. Animal and in vitro studies have begun to find links between insulin and mechanisms with clear pathogenetic implications for AD. In vitro, insulin modulates the concentration of Aβ, aggregation of which is a fundamental neuropathological hallmark of AD. For example, insulin promotes the release of intracellular Aβ in neuronal cultures, affecting both its short ($Aβ_{1–40}$) and long ($Aβ_{1–42}$) forms and accelerating their trafficking from the Golgi apparatus and trans-Golgi network to the plasma membrane.[66]

Insulin may also affect Aβ degradation via insulin degrading enzyme, a metalloprotease that catabolises insulin. Insulin degrading enzyme is strongly expressed in the brain as well as in liver, kidney, and muscle tissues[67] and may play a crucial part in Aβ clearance in the brain.[68–70] This enzyme has also been implicated in the regulation of intracellular degradation of Aβ, unlike the neutral endopeptidase neprilysin,[71] and in the degradation of the intracellular domain fragment of APP, which is produced by cleavage of APP by γ secretase.[72] Furthermore, decreased activity, low concentrations, and small amounts of mRNA of insulin degrading enzyme have been observed in brain tissue from patients with AD, and knockout mice that lack the enzyme have reduced degradation of Aβ and insulin in brain.[73–75] The induction of insulin resistance in transgenic T2576G mice, a model of AD, potentiated brain amyloidosis and lowered the amount of insulin degrading enzyme and concentrations of insulin in the brain.[76]

In vitro studies thus suggest that insulin may modulate Aβ release and degradation, as well as degradation of the APP C-terminal fragment. Because insulin promotes release of Aβ,[66] a high concentration of insulin in the brain caused by transport of insulin from the periphery may increase the amount of Aβ in extracellular compartments, such as the CSF. Similarly, a high concentration of insulin may inhibit the degradation of Aβ through competition as a target for insulin degrading enzyme. High plasma concentrations of insulin may also affect peripheral Aβ clearance, in effect obstructing the peripheral sink and resulting in high concentrations of Aβ in the brain. To investigate insulin effects in vivo in human beings, we examined differences in CSF concentrations of $Aβ_{1–42}$ in normal older adults after intravenous infusion of either insulin or saline.[77] Insulin infusion led to an increase in CSF concentrations of $Aβ_{1–42}$, which was most apparent in elderly individuals. As has been observed previously, insulin infusion facilitated declarative memory for the group as a whole, but such facilitation was attenuated in the older people with the greatest increase in CSF $Aβ_{1–42}$ concentrations. We speculated that this pattern may reflect that in younger adults, release of $Aβ_{1–42}$ is followed by its rapid and efficient clearance such that CSF $Aβ_{1–42}$ concentration does not change measurably. For some older adults, however, $Aβ_{1–42}$ is not cleared quickly, and sustained increases may affect memory facilitation. Thus for older adults with ineffective clearance mechanisms, as signified by higher $Aβ_{1–42}$ concentrations, insulin improvement of memory is opposed, resulting in an inverse correlation between insulin-induced memory facilitation and CSF $Aβ_{1–42}$. Several recent reports have also described inhibitory effects of peripheral and intracerebroventricular $Aβ_{1–42}$ on molecular and neurophysiological correlates associated with memory in rodents.[78–80] Some of these effects may be apparent within 1 h of $Aβ_{1–42}$ dose. It has been proposed that soluble Aβ assemblies disrupt memory acutely, purportedly through effects on long-term potentiation.[79,80] Taken together, these findings are consistent with the possibility that high $Aβ_{1–42}$ concentrations that are not lethal in neurons, such as those provoked by acute hyperinsulinaemia, may disrupt cellular functions related to memory, perhaps contributing to impaired memory before the formation of senile plaques.

Several studies have examined the effects of acute hyperinsulinaemia, showed the potential effect of insulin on Aβ concentrations, and shed light on why brain concentrations of insulin may actually be lower in some patients with AD.[62,64,76] Chronic peripheral hyperinsulinaemia has been associated with a pattern in which brain concentrations of insulin are initially high, then decrease as transport of insulin into the brain is downregulated. Consistent with this pattern, it has been shown that genetically obese Zucker rats have reduced binding of insulin to brain capillaries[81] and low hypothalamic insulin concentrations in comparison with lean controls.[82] Peripheral hyperinsulinaemia may also invoke a signal that inhibits synthesis of insulin in the brain. Thus low concentrations of insulin in the brain could reduce the release of Aβ from intracellular compartments into extracellular compartments for clearance. Intraneuronal accumulation of Aβ has been proposed as an initiating event in the pathogenesis of AD.[83] In addition, as noted, high plasma concentrations of insulin may interfere with degradation of Aβ that is transported out of the brain. Thus for some patients with AD, high peripheral and low brain concentrations of insulin would reduce clearance of Aβ both in the brain and periphery.

Insulin and other neuropathological mechanisms

A role for insulin has also been suggested for other AD-related mechanisms. Insulin inhibits phosphorylation of tau, which forms neurofibrillary tangles, a second neuropathological hallmark of AD. Insulin may affect tau through its regulation of glycogen synthase kinase 3β, a downstream target in the insulin signalling pathway.[84] Recent work also implicates *IRS2*; mice in which this gene has been knocked out have more tangles and hyperphosphorylated tau.[85] Other processes that may initiate, potentiate, or parallel amyloid and tau abnormalities in AD have been linked to insulin regulation. Inflammation has been proposed as a critical promoter of AD pathogenesis.[86] Insulin has long been known to play a part in peripheral response to inflammation. Insulin has anti-inflammatory effects at low doses during short-term inflammatory provocation.[87] During long-term hyperinsulinaemia or chronic inflammation, however, insulin may exacerbate the inflammatory response and increase

markers of oxidative stress. It promotes superoxide anion formation, inhibits degradation of proteins damaged by oxidation, and increases synthesis of polyunsaturated fatty acids, which are vulnerable to lipid peroxidation.[88] Insulin regulates prostaglandin production in adipose tissue,[89] and may thereby influence concentrations of eicosanoids such as F2 isoprostane. For example, hyperinsulinaemic Zucker rats have high eicosanoid concentrations compared with those in normo-insulinemic littermates.[90] In human beings, plasma concentrations of C-reactive protein and the proinflammatory cytokines interleukins 1β, interleukin 6 and TNF α were synergistically increased when insulin was given with the endotoxin lipopolysaccharide.[91]

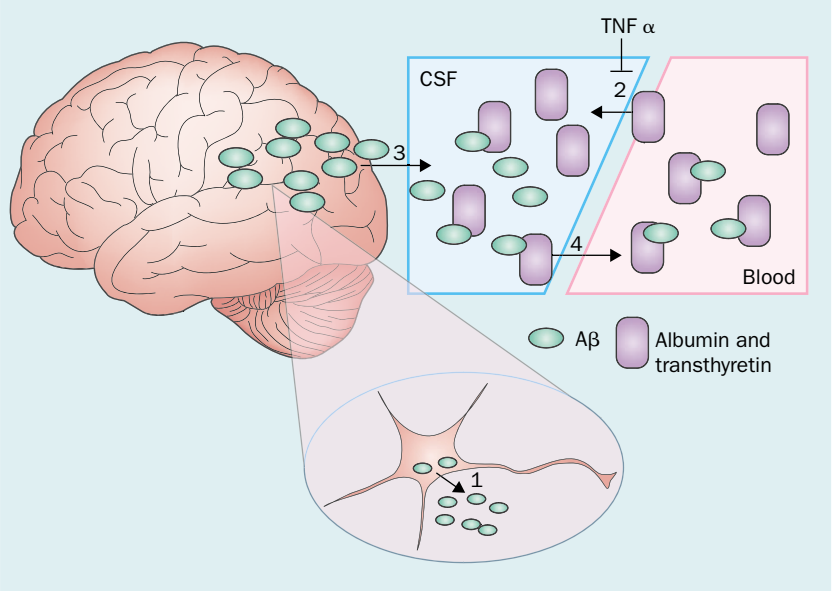

Figure 2. Regulation of cerebral Aβ clearance by insulin and insulin-like growth factor (IGF) 1. Insulin prevents the intraneuronal accumulation of Aβ by promoting its release (1). IGF 1 and insulin increase entry of carrier proteins such as albumin and transthyretin into the brain (2), where they bind to and transport Aβ into CSF (3) and blood (4). This process is inhibited by TNF α. Reproduced with permission from Elsevier.[104]

Insulin-related genes

Few studies have examined the linkage of insulin related genes to AD. Liolitsa and colleagues[92] examined genetic variations in the regulatory subunits of phosphatidylinositol-3 kinase and protein phosphatase 1, two central components of insulin signalling pathways. The researchers found an association between the p85α regulatory unit isoform of phosphatidylinositol-3 kinase and risk of AD in women who were not carriers of the *APOE* ε4 allele (OR=2·65). A second association between a protein-phosphatase-1 regulatory unit isoform and AD was not affected by sex or *APOE*. Both of these findings await confirmation in independent studies. Association with a locus on chromosome 10 in the region of the insulin-degrading-enzyme gene has been identified in several, but not all, studies.[93–98] Although no mutations have been identified, association with several polymorphisms in the insulin degrading enzyme has been reported that may be affected by *APOE* genotype. Edland and co-workers[99] showed that the C allele of *IDE3* was associated with a high risk for AD in people without *APOE* ε4. Ait-Ghezala and colleagues[94] found an association between the D10S583 polymorphic marker and AD, which replicated a previous report[93] in an independent sample; an interaction between *APOE* genotype and presence of the marker was observed. These findings are interesting in light of reports of that hippocampal expression of insulin degrading enzyme and insulin sensitivity differ according to *APOE* genotype in patients with AD.[74]

Insulin and other growth factors

An intriguing unanswered question is to what extent insulin's role in AD pathogenesis interacts with similar growth factors such as insulin-like growth factor 1 (IGF 1). Receptors for both insulin and IGF 1 have more than 50% amino-acid sequence homology and belong to the same family of tyrosine kinases; both receptors are composed of two extracellular subunits and two transmembrane subunits, and ligand binding initiates similar cellular signalling events for both proteins.[100,101] IGF 1 and insulin are thought to bind to both IGF 1 and insulin receptors, although the binding affinity is about 100 times greater when one protein binds to its respective receptor than when it binds to the other receptor.[100] With chronic high insulin concentrations, however, insulin is more likely to cross-react with the IGF 1 receptor, which results in activation of the IGF system. Furthermore, insulin and IGF 1 receptors can heterodimerise. Heterodimers containing the insulin receptor A isoform can bind and be activated by insulin or IGF 1. Insulin concentration and the relative amount of insulin receptor isoforms may then affect tissue specific responses to both insulin and IGF.[100] It has been suggested that insulin's actions are preferentially metabolic in nature whereas IGF 1 had more pronounced mitogenic effects.[102] The potential importance of IGF 1 was highlighted by findings that it increased Aβ clearance from brain to periphery in animal models, by upregulating the entry of carrier proteins across the blood–brain barrier, an effect that was blocked by raising the concentration of TNF α.[103] Gasparini and Xu[104] suggest that insulin causes release of intracellular Aβ, which then binds to IGF-1-induced carrier proteins and is transported from the brain (figure 2). Whether the role of insulin is restricted to Aβ release, or whether it may also affect carrier-protein-mediated transport—as insulin increases albumin transport[105] and has been shown to increase CSF Aβ concentrations in human beings[77]—is unclear. Which receptor insulin or IGF 1 use to exert their effects on Aβ clearance is also unknown.

Summary

In summary, evidence indicates an association between peripheral hyperinsulinaemia, insulin resistance, type-2 diabetes mellitus and hypertension, and increased risk of AD. Several studies have also replicated findings that insulin regulates amyloid concentrations in vitro and, more importantly, in vivo in human and mouse models. Both increased and decreased insulin concentrations have been proposed to promote AD pathogenesis through differing effects on Aβ release and clearance. Although studies suggest an effect of *APOE* genotype on insulin regulation, the nature of this effect and the mechanism associated with it have not been characterised. Finally, no AD-associated mutations in insulin-related genes have been identified and replicated in independent samples.

Vascular dementia

Insulin resistance and hyperinsulinaemia are well-established risk factors for vascular disease. In a recent review, Wheatcroft and colleagues[106] describe research that supports a primary role for hyperinsulinaemia and insulin resistance in endothelial dysfunction in part through its regulation of nitric oxide, reactive oxygen species, cytokines, and endothelin. Insulin resistance and type-2 diabetes mellitus are associated with increased risk of stroke and with worse outcome after stroke.[107] Essential hypertension, a risk factor for cognitive decline and dementia,[108] is commonly accompanied by insulin resistance; 30–50% of all patients with hypertension have insulin resistance, many of whom do not have diabetes. Hyperinsulinaemia is a predictor of impaired cognition in patients with hypertension who do not have diabetes. In a cross-sectional study comparing normotensive adults with people with hypertension (but not diabetes) with and without hyperinsulinaemia, cognitive performance was significantly low only in the hyperinsulinaemic-hypertensive group.[109]

In line with these findings, as discussed previously, several epidemiological studies have documented an increased risk for vascular dementia in patients with type-2 diabetes mellitus or hypertension.[51,54,110] Three studies have examined data from the Honolulu-Asia Aging Program, a longitudinal study of over 8000 Japanese-American men followed up over 25 years.[56,57,111] A high risk of vascular dementia in participants with diabetes or hyperglycaemia or hypertension was reported in all three studies, even after adjusting for numerous covariates such as body-mass index, lipid concentrations, education, and age. A study of 1789 Latin-American people reported that the risk of unspecified dementia increased eight times in participants with type-2 diabetes mellitus and stroke. In subanalyses the authors showed that diabetes was more common in patients with vascular dementia and in those with AD.[112] Carantoni and co-workers[113] found that fasting plasma concentrations of glucose and insulin were high in patients with vascular dementia and those with AD compared with those in healthy people. Given the growing awareness that vascular factors may contribute to AD, it is not surprising that many such studies have found diabetes and hyperinsulinaemia to be independently related to both disorders. One study suggested that the association is exclusive for vascular dementia in patients more than 80 years of age.[114] However, no neuroimaging of neuropathological validation was undertaken to support the accuracy of the diagnosis of vascular dementia, a particular problem given that neuropathological studies suggest that many older patients diagnosed with this disorder meet pathological criteria for AD.[48]

The importance of vascular factors in the pathogenesis of AD and the frequency with which vascular and AD pathology co-occur have become increasingly clear. The pattern of vascular injury commonly shared by the two disorders (microvascular disease, white-matter pathology, and lacunar infarction) has been causally linked to insulin resistance[115] as have inflammation and abnormalities of lipid metabolism, which raises the possibility that this shared pathological substrate underlies the overlap between the two syndromes.

Parkinson's disease

Several studies suggest a high prevalence of insulin resistance in patients with PD. As reviewed by Sandyk,[116] estimates of impaired glucose tolerance in this group range from 50–80%. Investigation of national survey data from 24 831 elderly adults filing Medicare claims found higher rates of diabetes and hypertension in adults with PD than in people without PD.[117] Few well-controlled human studies have been done in recent years. Interestingly, some drugs used to treat PD, such as levodopa, induce hyperglycaemia and hyperinsulinaemia, whereas others, such as bromocriptine, may increase insulin sensitivity.[118,119] These effects may obfuscate the interpretation of studies in which insulin function is assessed in treated patients. The defect in insulin action has, however, been shown to precede medication. Van Woert and Mueller[118] showed reduced insulin-mediated glucose uptake in newly diagnosed, never-treated adults with PD, whereas Boyd and colleagues[120] found inhibition of early insulin secretion and long-term hyperinsulinaemia and hyperglycaemia after glucose loading in a similar sample. Changes in insulin action do not seem to be caused by reduced physical activity.[121]

As with AD, the question has been raised as to whether vascular factors in disease pathogenesis could constitute one of the mechanisms through which insulin resistance increases the risk of PD. The syndrome of vascular parkinsonism has regained credibility as a diagnostic category that includes patients whose parkinsonism is accompanied by subcortical white-matter ischaemic lesions commonly in conjunction with basal ganglia or brainstem lacunae.[122] The few histopathological studies in these patients suggest preservation of dopamine-producing cells in the substantia nigra. Large consecutive autopsy series have indicated that about 3–6 % of patients with PD have vascular PD.[123] For the rest of patients with PD, there is some controversy as to whether the presence and type of cerebrovascular disease is high compared with healthy people. The largest such series compared 617 autopsy-proven cases of idiopathic PD with 535 age-matched control individuals.[124] The total frequency of cerebrovascular lesions including lacunae, amyloid angiopathy, white-matter lesions, old and recent ischaemic infarcts, and haemorrhages was slightly high in patients with PD (44·0% *vs* 32·8%).

Some theories propose that all patients with PD eventually become demented, but the rate at which the dementia occurs

differs among patients because of unknown factors. The association of insulin resistance and dementia in PD has not been examined carefully, and existing studies have produced inconsistent results. Some early studies found an increased risk of dementia in patients with diabetes and PD. Schwab[125] examined data from a series of 800 patients with PD and suggested that diabetes accelerated progression of both motor and cognitive symptoms. Sandyk and Awerbuch[126] assessed dementia with a bedside mini-mental state exam in 12 patients with PD, five of whom had diabetes. All five patients with diabetes had some degree of dementia, whereas none of the other patients did. The authors suggest that dementia in PD may be related to comorbid AD, an interesting possibility in light of the association between diabetes and the two disorders. Hypertension, which is commonly associated with insulin resistance, increased the risk of PD-related dementia in a case-control study.[127] By contrast, Levy and co-workers[128] examined whether self-reported diabetes and hypertension were associated with the development of dementia assessed through neuropsychological testing in a registry-derived group of 180 non-demented patients with PD. They found no association with these risk factors and development of dementia. Finally, no studies have determined whether insulin dysregulation also characterises patients with Lewy-body dementia.

The recent evidence supporting a role for insulin dysregulation in PD is largely indirect, or based on research in animals focused on relevant disease mechanisms. The primary neuropathological feature of PD is loss of dopaminergic neurons in the substantia nigra pars compacta, which affects both direct and indirect GABA inhibitory pathways to the internal globus pallidus and the substantia nigra reticulata. Dopaminergic neurons and insulin receptors are densely represented in the substantia nigra;[13,14] a fundamental defect in PD is the loss of these cells.[14] Loss of insulin-receptor immunoreactivity and mRNA and loss of tyrosine hydroxylase (the rate limiting enzyme in DA synthesis) mRNA in the substantia nigra have been also shown in neuropathological studies of patients with PD.[129,130] No abnormal CNS markers have been identified in vivo. Insulin concentrations in CSF were not different in patients with PD from those in an age-matched neurological comparison group.[131]

Studies in animals have reinforced the observation that dopaminergic drugs influence insulin production, insulin resistance, and glycaemic control. For example, intracerebroventricular delivery of bromocriptine, a potent D2 receptor agonist, improved insulin sensitivity in hamsters.[132] These findings prove that dopamine activity in the CNS contributes to peripheral insulin-mediated glucose metabolism. Insulin and dopamine may exert reciprocal regulation; for example, intracerebroventricular delivery of insulin increased the amounts of dopamine transporter mRNA and activity in the substantia nigra and in D8 cells.[133,134] By contrast, hypoinsulinaemia induced by streptozotocin decreased the amounts of dopamine transporter mRNA and tyrosine hydroxylase mRNA in the substantia nigra.[135] Consistent with these findings, hypoinsulinaemia resulting from streptozotocin-induced diabetes has been shown to decrease basal dopamine concentrations and amphetamine-induced dopamine overflow in the mesolimbic cortex.[136] Also, hypoinsulinaemic-diabetic rats, treated with alloxan or streptozotocin, showed increased striatal dopamine binding, which was normalised when alloxan-treated rats were given insulin.[137]

In summary, although clinical data suggest impaired glucose tolerance and insulin dysregulation characterise many patients with PD, few recent studies have carefully described the specific pattern of dysregulation, nor has a solid case been made for the role of insulin dysregulation independent of hyperglycaemia. Results from animal and in vitro studies, however, show a clear role for insulin in the regulation of brain dopaminergic activity. Loss of insulin-receptor immunoreactivity and mRNA and tyrosine hydroxylase mRNA in the substantia nigra have also been found in neuropathological studies of patients with PD.

Huntington's disease

As with PD, studies show that patients with HD have a higher prevalence of diabetes and insulin abnormalities but few recent well-controlled studies have been done. Podolsky and Leopold[138] did oral glucose tolerance tests and intravenous arginine tolerance tests on 14 patients with HD, and found that 50% of the patients had abnormal glucose tolerance characterised by hyperglycaemia and hyperinsulinaemia. Farrer[139] surveyed 620 people with HD, and found that 10·5% had diabetes, this exceeded age-matched population prevalence. Schobotz and colleagues[140] found that a third of patients with HD (sample size=25) had impaired glucose tolerance compared with 3% of their control group.

Clearly, the previous discussion of insulin's role in dopamine regulation has relevance for HD. In addition, animal models have suggested that impaired glucose metabolism in HD may be caused by impaired insulin gene expression. Studies with a transgenic HD mouse model that expresses a portion of the human huntingtin gene along with 140 CAG repeats have shown that these animals develop impaired glucose tolerance at 8 weeks of age and frank diabetes by 12 weeks of age.[141,142] Interestingly, the onset and progression of the glucoregulatory disturbance is similar to the onset of HD symptoms in these animals. Further examination has revealed low insulin gene expression in the pancreas of these transgenic animals, which was accompanied by high numbers of intranuclear inclusions and low concentrations of insulin and coactivators p300 and PDX 1.[142] The precise mechanism underlying low insulin gene expression is not clear, but may be related in part to the polyglutamine expansion characteristic of HD, as both Friedrich's ataxia and myotonic dystrophy, two other polyglutamine expansion disorders, are associated with insulin resistance and poor glucose tolerance. A disorder closely related to HD, dentatorubral-pallidoluysian atrophy (DRPLA) is caused by a CAG expansion in the *DRPLA* gene, the product of which, atrophin 1, interacts with the insulin-receptor tyrosine-kinase substrate protein IRSp53. This protein is a recently identified member of the insulin-receptor-substrate family with a very selective distribution in brain tissues, including frontal cortex, caudate nucleus, nucleus accumbens, and hippocampus (where it is colocalised with the insulin receptor). This pattern of

Panel 1. Insulin-related mechanisms shared by most neurodegenerative disorders

Decreased cerebral glucose metabolism
Increased inflammation
Increased oxidative stress
Increased advanced glycation end products
Increased vascular dysfunction
Decreased neurogenesis
Decreased neuronal repair

distribution fits closely with the brain regions most affected by DRPLA and HD, and provides a structure through which disrupted insulin signalling could affect a selective neuronal circuit.[143]

Insulin dysregulation and neurodegenerative disease: shared and specific mechanisms

As we learn more about the multifaceted role of insulin in the brain, we will be better able to identify the shared and specific contributions of insulin dysregulation to various neurodegenerative disorders. Some general mechanisms have obvious relevance to several disorders (panel 1). The interplay between insulin abnormalities and vascular function may be a converging mechanism in AD, vascular dementia, and PD. Insulin-mediated effects on brain vasculature could cause chronic hypoperfusion and energy depletion. Similarly, proinflammatory effects of prolonged hyperinsulinaemia may potentiate neurodegeneration. Other effects that are not restricted to vascular function may have general consequences. For example, abrogation of insulin's role in repair of injury or in promotion of neurogenesis may have widespread negative consequences for brain ageing. Hyperglycaemia accompanying insulin resistance may increase the presence and deleterious effects of advanced glycation end products, and many more such mechanisms could place an increasing burden on the ageing brain.

The complexity of insulin signalling pathways and the multiple points at which interference can affect their functions likely contributes to the general finding of insulin resistance in numerous ageing-related neurodegenerative disorders. Defects at different points in insulin signalling cascades may have disease-specific effects (panel 2). For example, reduced clearance of insulin by insulin-degrading enzyme may cause insulin resistance and increased accumulation of Aβ, whereas defects in glycogen-synthase kinase 3β feedback may impede downstream insulin effects and promote tau hyperphosphorylation. The specificity of insulin action is also affected by the signalling milieu, which in turn is determined by the cellular location in which signalling occurs, as well as by the presence or absence of various proteins and cofactors that interact in the signalling process. For example, lipid abnormalities may affect the composition of lipid-rich membrane microdomains in which many insulin-related signalling events are initiated. Differing distributions of insulin receptor substrate proteins could underlie regionally specific effects, as in the case of the IRSp53 protein and dentatorubral-pallidoluysian atrophy.

Whether insulin dysregulation merely superimposes the general consequences of disrupted energy metabolism, inflammation, oxidative stress, impaired injury response, and reduced neurogenesis on a pre-existing disease-specific neurobiological template, or whether disease-specific defects in insulin metabolism occur that make unique contributions to individual disorders, is unknown. Regardless of the specific cause, the improvement of insulin sensitivity and reduction of peripheral hyperinsulinaemia may have beneficial effects in various neurodegenerative disorders. Of interest, the thiazolidinediones or PPAR-gamma agonists improve insulin sensitivity and have anti-inflammatory effects. Clinical trials are underway to determine whether they may be beneficial in slowing the progression of AD, and investigation of their use in other neurodegenerative disorders seems warranted. Finally, much additional work is needed to elucidate the complex role of insulin in the normal ageing brain. With such knowledge in hand, we will be better able to understand, treat, and perhaps even prevent disorders in which insulin dysregulation is a causal or contributory factor.

Panel 2. Insulin-related mechanisms specific to individual neurodegenerative disorders

AD
Insulin promotes intraneuronal Aβ release and increases carrier protein entry into brain for Aβ transport.

High peripheral insulin concentrations:
inhibit peripheral Aβ degradation;
decrease number of insulin receptors in the BBB;
decrease concentrations of insulin in the brain;
decrease transport of carrier proteins.

Low brain insulin concentrations:
decrease release of intraneuronal Aβ;
decrease amounts of IDE;
increase tau hyperphosphorylation.

Possible genetic polymorphisms include:
IDE haplotype variants;
variants in the PI3K and PP1 regulatory subunits.

Vascular dementia
No specific mechanisms proposed.

PD
Insulin increases dopamine transporter mRNA in substantia nigra and regulates brain dopamine concentrations.

HD
Possible insulin-related abnormalities include a characteristic polyglutamine expansion, which may be associated with reduced insulin gene expression and modulation of IRSp53 protein activity.

BBB=blood–brain barrier; IDE=insulin degrading enzyme; IRS=insulin receptor substrate; PI3K=phosphatidyl inositol 3 kinase; PP1=protein phosphatase 1

Search strategy and selection criteria

Relevant studies were identified by searches of MEDLINE with the terms "insulin", "diabetes", "hypertension", and "vascular" combined with "AD", "PD", "HD", "vascular dementia", and "Lewy-body dementia". We searched from 1960 through 2003. Articles were also found by reviewing reference lists of papers identified by the above searches. Only papers published in English were included.

Authors' contributions

Both authors searched for relevant references and prepared this review.

Conflict of interest

SC is a consultant for GlaxoSmithKline, whose insulin-sensitising compound rosiglitazone is currently being tested in patients with AD. GlaxoSmithKline also provided partial funding for SC to do pilot trials of this compound in patients with memory impairment.

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