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Review Article

Insulin resistance and pathological brain ageing

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Abstract

Sir Harold Himsworth's prescient observations 75 years ago have recently been expanded to include a clear relationship between insulin resistance and central nervous system function. Insulin is a master regulator of corporeal ageing in all known species, determining the rate and expression of ageing in multiple body systems. Thus, it is not surprising that insulin also plays an important role in brain ageing and cognitive decline that is associated with pathological brain ageing. Brain ageing is accompanied by reduced insulin effectiveness, either by an inadequate cellular response to insulin or by insulin deficiency attributable to reduced insulin transport across the blood–brain barrier. Age-associated brain insulin abnormalities may contribute to cognitive decline in ageing, as have been documented in older adults with Type 2 diabetes mellitus and hypertension. With more extreme pathology, brain insulin resistance may be associated with neurogenerative diseases such as Alzheimer's disease, and the condition which precedes Alzheimer's disease, known as amnestic mild cognitive impairment. In the following review, we discuss the mechanisms through which insulin resistance may induce or potentiate pathological brain ageing and thereby create a neurobiological environment that promotes neurodegeneration and associated cognitive decline. This topic is timely, given that insulin resistance-associated conditions such as diabetes and obesity have reached epidemic proportions. The prevalence of such chronic conditions, in combination with a rapidly ageing population, may result in a corresponding increase in the prevalence of Alzheimer's disease and other cognitive disorders. Fortunately, insulin resistance-associated conditions are amenable to both pharmacologic and lifestyle interventions that may reduce the deleterious impact of insulin resistance on the ageing brain.

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Keywords brain, insulin resistance

Abbreviations apo, apolipoprotein; GLUT, glucose transporter; GSK, glycogen synthase kinase; PPARγ, peroxisome proliferator-activated receptor gamma; TNF, tumour necrosis factor

Insulin and the brain

The peripheral effects of insulin, a hormone secreted by pancreatic β-cells, have been well characterized. Recent evidence demonstrates that insulin is also active in the central nervous system. Although controversy exists as to whether insulin is synthesized in the adult brain, it is readily transported into the central nervous system across the blood–brain barrier by a saturable, receptor-mediated process [1–3]. Raising peripheral insulin levels acutely elevates brain and cerebrospinal fluid insulin levels, whereas prolonged peripheral hyperinsulinaemia down-regulates blood–brain barrier insulin receptors and reduces insulin transport into the brain [4,5]. Insulin receptors are located in the synapses of both astrocytes and neurons [6]. Although insulin and insulin receptors are abundant in the brain, they are selectively distributed, with high concentrations in the olfactory bulb, cerebral cortex, hippocampus, hypothalamus, amygdala and septum [2,7–9].

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Insulin and cognition

Insulin receptors are densely localized in the hippocampus and medial temporal cortex, areas which support memory. In rats, acute intracerebroventricular insulin administration improves memory on a passive-avoidance task [9]. In humans, acute intravenous insulin administration, while maintaining euglycaemia, reliably enhances story recall [10–13]. Intranasal insulin administration using specialized nose-to-brain delivery devices also enhances memory [14]. Conversely, learning may also influence insulin receptor expression and function. For example, training rodents on a spatial memory task increased insulin receptor expression in the hippocampal dentate gyrus and CA1 field [15]. Thus, the act of learning is accompanied by

changes in insulin signalling molecules in the hippocampus. Collectively, these studies suggest that insulin may contribute to normal memory functioning.

There are several mechanisms through which insulin may affect memory. One mechanism may be through effects on cerebral energy metabolism. Although insulin does not appear to influence glucose transport into the brain, it may have more selective effects on cerebral glucose metabolism. Bingham *et al*. [16] demonstrated an increase in cerebral glucose metabolism that was particularly pronounced in the cortex following administration of a low dose of insulin. The basis for regional insulin effects on glucose metabolism may be attributable to the distribution of glucose transporter isoforms (GLUTs) [17,18]. The insulin-sensitive GLUTs 4 and 8 are selectively distributed in the brain and insulin increases brain GLUT 4 expression and translocation [19]. In rats, GLUT 4 is expressed in the cerebellum, sensorimotor cortex, hippocampus, pituitary and hypothalamus [20–23] and GLUT 8 has been observed in the hippocampus and hypothalamus [17]. Notably, substantial co-localization exists for insulin-containing neurons, insulin receptors and GLUTs 4 and 8 [18,20]. These overlapping distributions are consistent with insulin-stimulated glucose uptake in selective brain regions, including medial temporal lobe structures that support learning and memory.

Other insulin-related mechanisms that are not directly related to modulation of glucose uptake have also been implicated in normal hippocampal functioning [24]. Long-term potentiation is a process of synaptic circuit remodelling thought to play a critical role in memory formation. Insulin may influence components of the long-term potentiation cascade, such as the cell membrane expression of NMDA receptors [25], which affect the likelihood of long-term potentiation induction. Insulin also modulates central nervous system levels acetylcholine and norepinephrine, neurotransmitters that are known to influence cognitive function [26,27] Thus, insulin affects numerous mechanisms relating to neuronal activity and cognitive function supported by such activity.

Insulin resistance and impaired cognition

In contrast to the beneficial effects of acute insulin elevations described above, insulin dysfunction resulting from insulin resistance and compensatory chronic elevations of circulating insulin may exert a negative influence on memory and other cognitive functions. For example, Type 2 diabetes has been associated with impaired learning in both animal and human studies [28]. Furthermore, impaired verbal memory has been observed in individuals with chronic hyperinsulinaemia in the absence of hyperglycaemia [29]. Additionally, impaired glucose tolerance has been associated with reduced hippocampal volume and memory impairment [30]. Taken together, these findings are consistent with the notion that acute and chronic hyperinsulinaemia have opposing effects on the neural substrates of memory. Chronic high levels of insulin and insulin resistance may exert a negative influence on several body systems, including the central nervous system, for some time prior to the onset of frank diabetes. There is increasing support that such early insulin abnormalities may be associated with the initiation of the cascade of Alzheimer's disease pathology in some individuals, years or even decades before the first clinical dementia symptoms are manifest.

Insulin abnormalities and Alzheimer's disease pathology

Converging evidence supports that the presence of insulin resistance raises the risk for developing Alzheimer's disease neuropathology. The manner in which insulin abnormalities may contribute to the symptoms and pathogenesis of Alzheimer's disease have been examined in a variety of experimental models. Hoyer and colleagues were the first group to suggest that desensitization of the neuronal insulin receptor plays a role in Alzheimer's disease [31]. In support of his theory, he and colleagues have demonstrated a reduction in insulin receptors and tyrosine kinase activity markers in Alzheimer's disease brain [32]. This initial finding has been confirmed and extended in a larger sample of patients, which demonstrated reduced insulin message with increasing Alzheimer's disease pathology and cholinergic deficit [33].

Animal and *in vitro* studies have documented relationships between insulin and mechanisms with clear pathogenic implications for Alzheimer's disease. *In vitro,* insulin modulates levels of the β-amyloid (A β) peptide, the aggregation of which is a fundamental neuropathological hallmark of Alzheimer's disease. For example, insulin promotes release of intracellular A β in neuronal cultures, accelerating their trafficking from the Golgi and trans-Golgi network to the plasma membrane [34]. Thus, low brain insulin may reduce the release of Aβ from intracellular to extracellular compartments.

Interestingly, Aβ also regulates brain insulin signalling. Soluble Aβ binds to the insulin receptor and disrupts its signalling capacity and long-term potentiation induction in mouse hippocampal slice preparations [35]. These effects could be prevented by exposing tissue to insulin prior to Aβ exposure. Synthetic soluble Aβ oligomers, down-regulate plasma membrane insulin receptors in primary hippocampal cultured neurons, leading to synaptic spine loss. This process was also prevented by pretreatment with insulin [36]. A related mechanism through which insulin and Aβ may interact to modulate Alzheimer's disease pathology is via synaptotoxic effects. Loss of synapses is the earliest structural defect observed in Alzheimer's disease. Soluble oligomeric species of Aβ are synaptotoxic, and insulin prevents binding of Aβ to synapses, thereby preserving synaptic integrity [36]. Insulin also reduced oligomer formation, which may have additional protective effects; a functional consequence of these effects appears to be protection against Aβ-induced disruption of long-term potentiation integrity, the process of synaptic remodelling believed to underlie memory formation [37]. Collectively, these findings suggest that soluble Aβ may induce neuronal insulin

resistance and synapse loss and that treatment with insulin, such as is provided by intranasal insulin therapy, may prevent these pathological processes.

A growing understanding of the importance of impaired Aβ clearance as opposed to increased Aβ production in late-onset Alzheimer's disease has created intense focus on mechanisms regulating Aβ degradation. Insulin may modulate Aβ degradation by regulating expression of the insulin degrading enzyme, a metalloprotease that catabolizes insulin [38]. The insulin degrading enzyme is highly expressed in brain as well as in liver, kidney and muscle [39] and may play a critical role in Aβ clearance in brain [40–42]. The insulin degrading enzyme has also been implicated in the intracellular degradation of Aβ [43]. Furthermore, decreased insulin degrading enzyme activity, levels and mRNA have been observed in Alzheimer's disease brain tissue and insulin degrading enzyme knockout mice have reduced degradation of Aβ and insulin in brain [44–46]. Thus, low central nervous system insulin may reduce insulin degrading enzyme levels in brain and thereby impair Aβ clearance.

Chronic peripheral hyperinsulinaemia may thus lower brain insulin levels and interfere with peripheral Aβ clearance. Chronic peripheral hyperinsulinaemia has been associated with a pattern in which brain insulin levels are initially higher, then decrease as transport of insulin into the brain is down-regulated [47]. Consistent with this pattern, it has been shown that genetically obese Zucker rats have reduced insulin binding to brain capillaries [4] and reduced hypothalamic insulin levels [48] in comparison with lean controls. Additionally, in a canine model of diet-induced insulin resistance, brain uptake of labelled insulin was reduced and peripheral insulin clearance was inhibited[49]. Adults with Alzheimer's disease show lower cerebrospinal fluid insulin levels, higher plasma insulin levels and reduced cerebrospinal fluid–plasma insulin ratios compared with healthy control subjects. High plasma insulin levels may interfere with degradation of Aβ transported out of the brain, thereby obstructing a peripheral Aβ-clearing 'sink'. Concomitantly, low brain insulin levels reduce release of Aβ from intracellular compartments into extracellular compartments where clearance is believed to occur. Thus, for some patients with Alzheimer's disease, high peripheral insulin levels and low brain insulin levels would result in reduced clearance of Aβ both in brain and in the periphery (Fig. 1).

Support for the validity of this model is provided by a recent study that induced insulin resistance in the T2576 mouse model of Alzheimer's disease with a high-fat diet. Diet manipulation resulted in a metabolic profile of high peripheral insulin and low brain insulin and insulin degrading enzyme levels compared with Tg2576 mice fed a normal diet [50]. Diet-induced insulin resistance caused twofold increases in Aβ40 and 42, and earlier, larger Aβ deposits compared with non-insulin-resistant Tg2576 mice. Furthermore, insulin-resistant mice had impaired learning on a water maze test. In another model of insulin resistance, APP/PS1 mice were given sucrose-sweetened beverages and also demonstrated increased brain Aβ deposition and reduced Morris water maze learning [51]. Together these results suggest that insulin resistance can precipitate the neuropathological and behavioural features of Alzheimer's disease and that raising brain insulin levels may reduce neuropathological changes related to Alzheimer's disease.

A role for insulin has also been suggested for other Alzheimer's disease-related mechanisms. Insulin inhibits phosphorylation of tau, the protein that forms neurofibrillary tangles, a second neuropathological hallmark of Alzheimer's disease. Insulin may affect tau through its regulation of glycogen synthase kinase (GSK)3β, a downstream target in the insulin signalling pathway [52]. Schubert and colleagues [53] abolished insulin signalling *in vivo* with a conditional knockout mouse model in which the insulin receptor gene was inactivated in the central nervous system. Phosphorylation of GSK 3β and protein kinase B (Akt) was reduced and phosphorylation of tau increased 3.5-fold. Recent work also implicates insulin receptor substrate 2, in that mice in which this gene has been knocked out have increased tangles and hyperphosphorylated tau [54].

Insulin resistance-related conditions and dementia

The above research provides compelling evidence concerning insulin's role in the central nervous system and the connection between impaired insulin action and the pathology that underlies Alzheimer's disease. The association between dementia and insulin resistance is further substantiated by investigations of conditions related to insulin dysfunction. Insulin resistance is a primary underlying cause of multiple chronic diseases and, as such, a likely key risk factor for dementia. However, because insulin resistance is rarely identified in its earliest stages and independent of these conditions, it is seldom incorporated

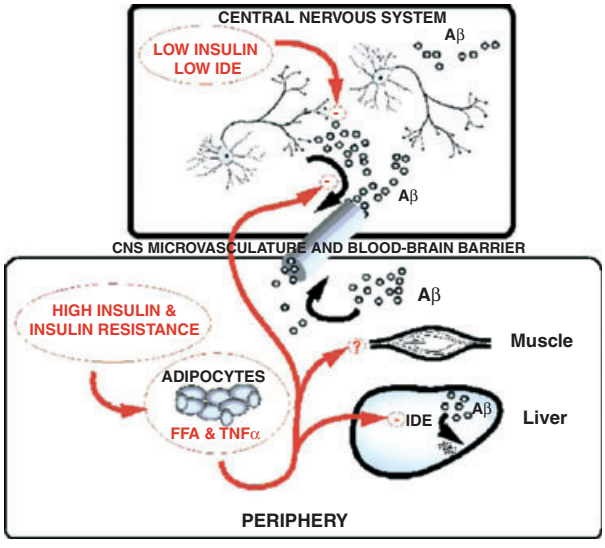

FIGURE 1 Model of peripheral hyperinsulinaemia, insulin resistance and Alzheimer's disease pathological processes. CNS, central nervous system; IDE, insulin degrading enzyme.

as a primary variable of interest in population-based models. Here, we focus on the increased dementia risk associated with insulin resistance-related syndromes, including diabetes, hyperlipidaemia, hypertension and obesity.

Diabetes

Diabetes is a strong predictor of cognitive decline in older adults [55,56] and multiple population-based studies have reported an association between insulin resistance and cognitive impairment in elderly populations [57–64]. Type 2 diabetes confers a significantly increased risk of dementia (both Alzheimer's disease and vascular dementia), a relationship that has been consistently reported in the literature [65–70]. For example, in the prospective, community-based Rotterdam study, Ott *et al.* [71] found that Type 2 diabetes significantly increased the risk for all-cause dementia and Alzheimer's disease, with greater risk apparent in people who were insulin-treated (and therefore likely to be in the more severe stages of the disease) at baseline. Similar results were reported by Leibson *et al.* [72] and the Religious Orders Study reported a 65% increased risk for Alzheimer's disease among those with Type 2 diabetes [73]. Findings from the Mayo Clinic Alzheimer's Disease Patient Registry show an increased prevalence of Type 2 diabetes (35 vs. 18% in non-demented control subjects) and impaired glucose tolerance (46 vs. 24%) for patients with Alzheimer's disease [74]. Further, Alzheimer's disease risk is raised independently from vascular dementia or other dementias [67,75], a finding that is not surprising given the wealth of literature that connects insulin dysfunction with Alzheimer's disease-specific brain pathology. Interestingly, dementia risk does not appear to be associated with the age at which diabetes is diagnosed [76].

Coupled with animal and *in vitro* studies that support the influence of insulin on Alzheimer's disease pathophysiological processes, the above epidemiological evidence provides further support for the association between diabetes and dementia. Recent neuropathological studies, however, have produced interesting and somewhat conflicting results. For example, dementia patients with treated diabetes had Aβ plaque loads that were similar to those of non-demented control subjects, while dementia patients with untreated diabetes had plaque loads consistent with dementia patients without diabetes [77]. Patients with treated diabetes with dementia had higher levels of microvascular infarcts and anti-inflammatory markers to a degree not present in patients with untreated diabetes [78]. Given the preliminary nature of these results and small sample sizes, these studies must be replicated prior to making any firm conclusions as to their meaning. If supported by larger studies, however, these findings could bring into question the relative impact of both Aβ and microvascular disease in the development of clinical dementia symptoms. It is possible that patients with treated diabetes, who are likely to be at a more advanced stage of disease, are more susceptible to lower levels of amyloid burden when they occur in the context of microvascular damage. Future neuropathological studies that carefully examine disease duration, treatment duration and dose, and concomitant vascular risk factors will certainly help to clarify these questions.

Dyslipidaemia

Insulin is a key modulator of lipid metabolism, and insulin resistance is associated with dyslipidaemia, a process that may represent yet another pathway by which insulin potentially exacerbates pathological Aβ processes in the brain. Although the mechanisms underlying the association between lipids, lipoproteins and Aβ are not well understood, it is increasingly clear that these interactions play a vital role in Aβ production and clearance. Animal models show greater VLDL secretion in advance of Aβ deposits in the brain [79] and Alzheimer's disease is associated with increased postprandial chylomicron and LDL levels [80]. Lipoproteins, including apolipoproteins E and J (apoE and apoJ), appear to play a significant role in mediating central nervous system Aβ transport and clearance. For example, highly lipidated apoE increases Aβ clearance and thus reduces amyloid deposition in the brain, while poorly lipidated apoE increases amyloid burden [81]. In the periphery, the Aβ clearance may also be mediated by apoE, apoJ and lipoprotein receptor-related protein-2 [82]. Inhibition of peripheral Aβ clearance may in turn lead to increased accumulation of Aβ in the brain.

Given the above results, it is not surprising that a relationship between hyperlipidaemia and Alzheimer's disease has been postulated. However, the connection between cholesterol and dementia is complex. High plasma cholesterol at midlife is associated with higher Aβ40 levels [83] and a 2- to 3-fold increased risk for later Alzheimer's disease dementia [84]. Conversely, total cholesterol in late life does not appear to be associated with Alzheimer's disease risk [84] and may in fact be protective to some degree [85,86]. In addition, despite the relationship between hyperlipidaemia and vascular dysfunction, high total cholesterol has not been linked with an increased risk for vascular dementia in either mid or late life [84]. Further investigation into the complex role of cholesterol, Aβ and dementia is thus warranted.

Hypertension

Through both direct effects and insulin resistance-related dyslipidaemia and inflammation, insulin dysfunction can substantially impact the vasculature. Insulin mediates capillary recruitment, vasodilation and regional blood flow [87,88]. Insulin resistance-associated declines in nitrous oxide and increases in endothelin-1 activity results in vasoconstriction and reduced blood flow. In the brain, such vasoconstriction and reduced capillary recruitment may ultimately impede neural activity and thus negatively impact cognitive function.

Approximately one in three adults have hypertension [89] and 50% of hypertensive patients are insulin resistant [90]. Hypertension impairs neuron-dependent blood flow (known as functional hyperaemia) via a number of insulin resistance-related processes, including oxidative stress, dysregulation of vasoactive

mediators (including nitrous oxide and endothelin-1), structural alteration of the blood vessels and insufficient cerebral autoregulation [91]. Animal models evidence increased Aβ deposition with hypertension, which leads to vascular dysfunction and reduced functional hyperaemia [91]. In population-based studies, hypertension at midlife is a risk factor for Alzheimer's disease and vascular dementia, lower brain weight and Aβ plaque load [92–95]. As with total cholesterol, however, studies examining the effects of late-life hypertension on dementia are mixed and blood pressure may in fact decline in the years prior to and following clinical dementia diagnosis [96].

Obesity

Obesity is a growing and dangerous epidemic in the USA and is closely linked to insulin dysregulation; 80% of obese individuals are insulin resistant [97]. Insulin typically inhibits adipocyte lipase action, which decreases the release of free fatty acids from adipose tissue. With obesity and insulin resistance, however, this process is disturbed and leads to chronically elevated free fatty acids [97]. Free fatty acids are linked to Alzheimer's disease pathology through a number of potential mechanisms, including inducing inflammation, promoting Aβ deposition and inhibiting Aβ clearance. Elevated free fatty acids inhibit the insulin degrading enzyme, which is both essential for normal insulin signalling and vital for Aβ clearance [98]. Further, free fatty acids promote the development of amyloid and tau filaments *in vitro* [99,100]. Free fatty acids also induce inflammation, particularly through interactions with tumour necrosis factor alpha (TNF-α), an inflammatory cytokine that has been implicated in Alzheimer's disease pathogenesis, particularly Aβ accumulation in brain [101–103]. TNF-α is overexpressed in adipose tissue of obese animals and humans, whereas neutralization of TNF-α increases insulin sensitivity and decreases plasma free fatty acid levels [104].

Despite the associations between obesity and the mechanistic processes leading to Alzheimer's disease pathology, the connection between obesity and dementia risk is not entirely clear [65]. Although associated with other insulin resistance-related conditions, including diabetes, hypertension and poorly controlled lipids, midlife obesity appears to confer a risk for later dementia over and above these factors [105–107]. Evidence concerning the effects of late-life adiposity on dementia risk is less clear, however [107], and individuals typically begin to lose weight with the onset of dementia. Despite conflicting literature in this area, however, it is likely that targeting the obesity epidemic across the lifespan would have substantial beneficial effects on overall health status and cognitive function.

Insulin resistance-related conditions: conclusions

For many of the insulin resistance-related conditions described above, it is becoming increasingly apparent that dementia risk is particularly elevated when such disorders are present during midlife. The reasons for this association are not entirely known; however, the neuropathological conditions associated with later dementia begin many years prior to the onset of the clinical dementia syndrome. Risk for chronic disease increases substantially at midlife and may set in motion the pathological processes responsible for late-life dementia. Interestingly, diabetes even in late life increases dementia risk, a finding that underscores the likely presence of subclinical impaired glucose tolerance resulting from insulin resistance for years prior to the onset of the disease.

Insulin resistance and Alzheimer's disease: preventative and therapeutic approaches

Pharmacologic insulin sensitization

Given the relationship between insulin resistance and memory impairment, therapeutic strategies aimed at treating early Type 2 diabetes may also benefit those patients with mild cognitive impairment or Alzheimer's disease. Peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists improve insulin sensitivity, decreasing circulating insulin and increasing insulin-mediated glucose uptake, with minimal risk of hypoglycaemia [108]. PPAR-γ activity may also reduce both Aβ accumulation and inflammation and thereby protect against neurotoxicity [109–111]. PPAR-γ agonists inhibit Aβ-stimulated secretion of pro-inflammatory products and decreased oxidative stress in both *in vitro* and *in vivo* models [112,113]. PPAR-γ agonists are thus attractive candidates for the treatment of insulin resistance and inflammation associated with early cognitive decline.

Rosiglitazone, a compound that binds with high affinity to PPAR-γ [114], has been used as an anti-diabetic insulin sensitizer. Rosiglitazone normalizes the insulin response and ameliorates the associated impaired stress response in Alzheimer's disease mouse models [115]. We conducted a parallel group, double-blind, placebo-controlled trial to test the hypothesis that treatment with rosiglitazone would produce beneficial cognitive effects for patients with amnestic mild cognitive impairment and early Alzheimer's disease [116]. Participants received a daily dose of 4 mg of rosiglitazone (n = 20) or matched placebo (n = 10) for 6 months. Delayed memory was preserved and attention improved over the 6-month trial for the rosiglitazone-treated group, whereas the placebo-assigned group showed the expected decline in performance. The degree of memory preservation was related to treatment response as indexed by fasting plasma insulin levels at 6 months. Plasma Aβ levels declined over the 6-month treatment period for the placebo-treated patients and remained stable in the rosiglitazone-treated group. Despite these promising results, a subsequent Phase III trial conducted by GlaxoSmithKline failed to show a benefit of 2, 4 or 8 mg of rosiglitazone over a 6-month period. These negative results, coupled with concerns about possible negative cardiovascular effects of rosiglitazone, have dampened enthusiasm for its use as a therapeutic agent for Alzheimer's disease. However, the thiazolidinedione

pioglitazone remains an attractive candidate and is currently being investigated in a Phase III trial.

Intranasal insulin

Insulin and its signalling markers are reduced in the central nervous system in Alzheimer's disease. Multiple studies demonstrate that supplementing insulin through intravenous administration (while maintaining euglycaemia) acutely increases central nervous system insulin and reliably improves cognition [10,11,117]. However, chronic peripheral insulin administration is not a viable therapeutic option because of risks associated with hypoglycaemia. In addition, it is likely that such an approach would exacerbate peripheral hyperinsulinaemia, with possible negative effects on Aβ clearance. Any long-term treatment strategy for normalizing central nervous system insulin levels in persons with Alzheimer's disease must avoid significantly increasing insulin in the periphery. Such an approach is possible with an intranasal administration technique.

Intranasal pathways to the central nervous system

The nasal cavity is unique in that olfactory sensory neurons are directly exposed to the external environment in the upper nasal cavity, while their axons extend through the cribriform plate to the olfactory bulb. Following intranasal administration, low molecular weight drugs can be directly transported to the central nervous system, bypassing the periphery. Several extraneuronal and intraneuronal pathways from the nasal cavity to the central nervous system are possible. The extraneuronal pathways rely on bulk flow transport through perineural channels to the brain or cerebrospinal fluid. In recent studies, labelled intranasal insulin or a closely related peptide, insulin-like growth factor-I (IGF-I), were administered to rodents [118,119]. Within 30 min, an IGF-I signal was detected along olfactory and trigeminal channels, with robust signal evident in hippocampus, amygdale and cortex. An additional extracellular pathway was identified with quick access to the cerebrospinal fluid after absorption into the submucosa along the olfactory nerve and cribriform plate [119–121]. These extracellular pathways provide direct access to the central nervous system within minutes of intranasal administration. Additionally, an intraneuronal pathway delivers drugs to the central nervous system hours or days later. Anterograde axoplasmic transport within olfactory sensory neurons has been demonstrated.

Intranasal insulin effects in the central nervous system

Several studies have examined the effects of intranasal insulin in human and animal models. Kern and colleagues [120] administered 40 IU of insulin intranasally in young, healthy adults. Cerebrospinal fluid and blood were sampled every 10–20 min for 80 min following administration. Insulin treatment resulted in increased cerebrospinal fluid insulin levels within 10 min of administration compared with placebo, with peak levels noted within 30 min. Cerebrospinal fluid insulin levels remained elevated for the 80-min study. Blood glucose and insulin levels did not change, demonstrating that the effects in cerebrospinal fluid are not attributable to transport from the nasal cavity to the systemic circulation. This is consistent with a large literature that demonstrates insulin's poor transport from the nasal cavity into blood [122]. Although elevated cerebrospinal fluid insulin levels do not conclusively demonstrate that brain insulin levels are similarly elevated, animal studies have shown significant drug uptake to the hippocampus and cortex. Francis *et al*. showed that intranasal insulin reversed the effects of diabetes in a murine model, reducing brain atrophy, increasing markers of synaptic function, increasing insulin receptors and phosphorylation, reversing diabetes-related reductions in choline acetyltranferase levels, reducing neuronal NFκB activation and increased activation of Akt, cAMP response element binding protein and GSK3β. These multifaceted effects were accompanied by a striking preservation of memory as measured by the Morris Waster Maze and radial arm tasks [118].

Functional and cognitive studies of the acute and chronic effects of intranasal administration also support insulin's transport to the central nervous system. Sixty minutes of intranasal insulin treatment (20 IU every 15 min) induced changes in auditory-evoked brain potentials (AEPs) compared with placebo [123]. We have also demonstrated that intranasal insulin acutely improves verbal memory in memory-impaired persons without affecting plasma insulin or glucose levels [124]. Memory impaired and normal adults received saline and four doses of intranasally administed regular insulin (10, 20, 40 or 60 IU insulin) on separate mornings. Per cent change in memory (story recall) relative to the placebo condition was enhanced for the three lower doses for the memory-impaired group.

With respect to effects of chronic intranasal insulin administration, several studies reported that 2 months of daily insulin administration (4×40 IU/day) significantly improves verbal memory and enhanced mood in young healthy adults [125,126]. In a recent pilot clinical trial we examined the effects of short-term daily intranasal insulin administration in 25 adults with Alzheimer's disease or mild cognitive impairment, who were randomly assigned to receive insulin (20 IU twice daily; $n = 13$) or placebo ($n = 12$) for 21 days. Relative to their baseline performance, insulin-treated subjects had improved memory and attention at day 21 than did placebo-assigned subjects.

In a recently-concluded trial, we extended these preliminary findings and examined the effects of two doses of intranasal insulin (20 and 40 IU) compared with placebo administered for 4 months to 104 adults with Alzheimer's disease or mild cognitive impairment [127]. Improved delayed memory was observed for the 20-IU group and performance preserved on other measures of cognition and daily function for both insulin-treated groups over the 4-month period. For a subset of participants who received F-18 fluorodeoxyglucose (FDG)

positron emission tomography, cerebral glucose metabolism declined for the placebo group and remained stable or improved for both insulin-treated groups. These two studies provide the first evidence of cognitive improvement following daily intranasal insulin administration for patients with early Alzheimer's disease and support brain insulin signalling as a promising target in the search for new therapeutic avenues in Alzheimer's disease.

Lifestyle modification: strategies for prevention

Although mediated by genetic influences, insulin resistance occurs largely as a result of lifestyle factors, including hypercaloric diets high in simple carbohydrates and saturated fats, and physical inactivity. Implementation of intervention programmes that address these challenges could significantly reduce the social and economic burden associated with late-onset dementia. Here, we examine two promising non-pharmacological strategies aimed at reducing pathological processes associated with ageing and dementia: diet modification and physical exercise.

Diet modification

A typical 'Western' diet consists of high levels of saturated fats and simple carbohydrates, a pattern of consumption that substantially raises the risk of insulin resistance, Type 2 diabetes, obesity, cardiovascular disease and hypercholesterolaemia [128–130], as well as the likelihood for cognitive impairment and Alzheimer's disease [131–135]. Conversely, improving the dietary profile to include reduced saturated fat and increased mono- and polyunsaturated fats may produce protective effects on cognitive functioning and Alzheimer's disease risk [131–134]. Animal models that examine the effects of diet intervention on Alzheimer's disease neuropathology have demonstrated that diets high in either saturated fat or sucrose modify processing of the amyloid precursor protein from which the Aβ peptide is produced, increase Aβ-related cerebrovascular disturbance and reduce brain insulin signalling and expression of the insulin degrading enzyme [136,137]. This section highlights the emerging support from recent human studies that suggest dietary intervention may play a key role in the prevention and treatment of cognitive decline in ageing.

Dietary patterns, cognition and dementia risk

Evidence from population-based studies generally supports that improved dietary profile leads to a reduced risk of age-related cognitive decline and dementia. These studies often focus on specific dietary elements and the role of fatty acids has received particularly close attention. For example, greater fish consumption and overall polyunsaturated fat intake has been associated with both improvements in cognition and reduced Alzheimer's disease risk; conversely, high saturated and trans-unsaturated fats are associated with worse cognition, greater decline and increased Alzheimer's disease and vascular dementia risk [138].

Despite the overall promising epidemiological support, not all longitudinal studies have found an association between fat intake profile and cognitive decline or dementia risk [139]. In addition, large clinical trials that incorporated specific fatty acids have generally failed to produce substantial positive results [140]. It has thus been postulated that a 'whole diet' approach, which mimics overall nutritive consumption patterns, may be a more useful and valid method of study. For example, the 'Mediterranean diet', which emphasizes consumption of complex carbohydrates, unsaturated fats and fruits and vegetables, and is low in saturated fats and simple carbohydrates, has received a great deal of attention for its association with reduced risk for both Alzheimer's disease and mild cognitive impairment [141–143]. In a recent controlled intervention trial aimed at examining the effects of diet on cognitive function and cerebrospinal fluid biomarkers in older adults with and without cognitive impairment, subjects were assigned to a 4-week isocaloric diet that consisted of either high saturated fat/high simple carbohydrates (a pattern associated with Type 2 diabetes and insulin resistance) or low saturated fat/low simple carbohydrates [144]. The diets produced pronounced changes in cerebrospinal fluid biomarker profiles, modulating levels of Aβ and the oxidative injury marker F2-isoprostane, and the low saturated fat/low glycaemic index diet was associated with improved memory. Taken together, these animal, population-based and human intervention studies suggest that dietary factors may influence the expression of Alzheimer's disease.

Physical exercise

A sedentary lifestyle is likely a key factor in the increase in insulin resistance-related conditions noted in recent years. Aerobic exercise, known to be an effective treatment for diabetes and related conditions, also has potent salutary effects in the brain [145,146]. Increased physical activity is consistently linked with improved learning and memory both in humans and in animal models [147]. The favourable effects of exercise are likely exerted through multiple pathways known to be influenced by insulin resistance, including improved cardiovascular and cerebrovascular function [148,149], anti-inflammatory processes [150,151] and enhanced insulin-dependent energy metabolism [152]. Thus, aerobic exercise has the potential to modify multiple processes compromised in pathological brain ageing. In the following sections, we review the evidence supporting a protective role of physical exercise intervention on dementia risk throughout the lifespan.

Lifetime exercise and dementia risk

Observational studies suggest that moderate physical activity throughout the lifespan is associated with improved cognitive function and reduced dementia risk in older age. For example,

self-reported lifelong moderate exercise was associated with improved working memory, processing speed and global intelligence in post-menopausal women [153]. Regular exercise during midlife, when many pathological disease processes likely begin, has been linked to reduced dementia risk and improved cognitive profile in older adults [154,155]. Long-term exercise has been shown to impact Alzheimer's disease pathology as well. In a recent study, older adults who exercised at least 30 min per day, 5 days per week for at least 10 years demonstrated lower brain Aβ deposition [using Pittsburgh compound B, PiB, on positron emission tomography (PET) scan] [156]. Animal models suggest that the benefits of aerobic exercise may begin early during the course of development by boosting neural reserves at a young age [157,158]. Human studies that rely on retrospective self-report have connected level of physical activity during adolescence and young adulthood to higher global cognitive functioning in women and improved processing speed in men during older age [153,159]. Taken together, these results suggest that a consistent lifelong exercise routine is likely an important component in the primary prevention of cognitive decline and dementia.

The impact of exercise during older age

Exercise and normal ageing: risk reduction

Physical activity during older age is associated with improved cognitive functioning in areas commonly affected by the normal ageing process, including processing speed, executive function and memory [145,160–165]. Numerous large-scale epidemiological studies provide evidence that links physical activity in older adults with reductions in the cognitive decline experienced by non-exercisers [166–169]. Although large-scale exercise intervention trials have yet to be completed, smaller trials demonstrate that aerobic exercise has particularly significant effects for cognitive processes related to executive functions, including selective and divided attention. These results are seen in both healthy and pre-diabetic older adults [145,170]. Further, imaging studies demonstrate that exercise interventions result in reductions in age-related volume loss [171,172] and more efficient brain activity in executive networks [173]. Indeed, 12 months of exercise training increased hippocampal volume significantly, reversing age-related decline by approximately 2 years [174]. Interestingly, some have suggested that older adults may derive even more benefit from exercise than younger adults with regard to improved cerebral vascular tone [175] and reduced cognitive decline [176].

Exercise and cognitive impairment: disease intervention

Recently, physical exercise has received attention as a potentially effective non-pharmacological strategy to prevent or slow decline in older adults already experiencing mild cognitive changes [177]. Although there are a limited number of intervention trials that specifically target mild cognitive impairment, initial results from studies that include moderate- to high-intensity exercise interventions present promising results. In a small, randomized, controlled 6-month trial of aerobic exercise vs. a stretching control condition for sedentary adults with mild cognitive impairment [178], Baker *et al.* [165] found that the aerobic exercise condition improved cardiorespiratory fitness, increased insulin sensitivity, reduced plasma Aβ levels and augmented performance on multiple executive function tasks. In a 6-month, randomized, controlled trial [179], subjects who exercised at a moderate intensity level demonstrated significant improvements on the Alzheimer Disease Assessment Scale (Alzheimer's diseaseAS-Cog). Despite these positive findings, however, another recent study that employed a multi-modal exercise programme for older adults with mild cognitive impairment who lived in a structured living environment failed to show improvements in cognitive function despite an enhanced cardiovascular profile [180]. The reason behind this discrepancy is not clear, but may suggest that, as cognitive impairment progresses and a greater level of structure is required, individuals may benefit to a lesser degree from exercise intervention. These findings may thus have important implications for the potential of exercise to mediate cognition as neuropathological Alzheimer's disease processes progress. Despite a favourable relationship between cardiorespiratory fitness and parietal and medial temporal lobe volume in patients with Alzheimer's disease [181], the small number of exercise intervention trials completed to date do not provide support for improvements in cognitive abilities once clinical Alzheimer's disease dementia is diagnosed [182]. A confounding factor, however, is the degree to which a moderate level of intensity may be achieved in these studies.

Summary

Himsworth's astute observations 75 years ago regarding the clinical manifestations accompanying differences in insulin sensitivity remain remarkably relevant today, and have expanded to encompass factors related to brain ageing and neurodegenerative disease. This expansion has led to the identification of novel mechanisms that may contribute to the pathogenesis of conditions such as Alzheimer's disease and, subsequently, to a new array of therapeutic targets. The concurrent increase in the ageing population and in the prevalence of insulin resistance raises the specter of a rapid escalation in the incidence of dementia. Fortunately, insulin resistance and related factors that predispose the central nervous system toward Alzheimer's disease pathology are responsive to lifestyle modification, offering a clear avenue to prevention. Unlike many pharmacologic treatments, lifestyle intervention strategies have pleiotropic effects and, as such, may be more efficacious for treating multifactorial diseases such as Alzheimer's disease. Alzheimer's disease pathology begins many years prior to clinical symptomatology; thus, strategies that focus on a 'lifespan approach' may achieve greater success than tertiary pharmacologic interventions to reduce the terrible burden of dementia to families and society. Although it is not likely that Himsworth envisioned this goal directly, if

accomplished it will become one of the most important facets of his legacy.

Competing interests

S. C. received an investigator-initiated grant from GlaxoSmithKline to study rosiglitazone and mild cognitive impairment. She has also served as a paid consultant for GlaxoSmithKline and Takeda Pharmaceuticals.

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