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**Cerebral ageing-the role of insulin and insulin-like growth factor signalling: A review**

Romain G *et al.* Cerebral ageing and insulin signalling

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**Abstract**

Cerebral ageing is a complex biological process associated with progressing cerebrovascular disease and neuronal death. It does not always, however, associate with a functional decline as the ageing mammalian brain retains considerable functional plasticity, which supports successful cerebral ageing where age-related cognitive decline is modest. On the contrary, pathological cerebral ageing results in memory impairment and cognitive deterioration, with Alzheimer’s disease being a florid example. Trophic/growth factors promote brain plasticity and among them are peptides which belong to the insulin family. Preclinical research suggests that the evolutionarily conserved brain insulin/insulin-like growth factor IGF-1 signalling system controls lifespan and protects from some features of Alzheimer’s disease such as neurodegeneration-related accumulation of toxic protein and cognitive deficiencies, as observed in animal models. Insulin and IGF-1 activate cell signalling mechanisms which play protective and regenerative roles; abnormalities in the insulin/IGF-1 system may trigger a cascade of neurodegeneration in Alzheimer’s disease. Alzheimer’s disease patients show cerebral resistance to insulin which associates with IGF-I resistance and dysregulation of insulin/IGF-1 receptors as well as cognitive deterioration. This review is focused on the roles of the insulin/IGF-1 signalling system in cerebral ageing and its potential involvement in neurodegeneration in the human brain as seen against the background of preclinical evidence.

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**Key words**:Brain; Insulin; Insulin receptor; Insulin-like growth factor; Longevity; Alzheimer’s; Diabetes mellitus; Inflammation

**Core tip:** Age itself is a major risk factor for the development of age-related cognitive decline, Alzheimer’s and cerebrovascular diseases. Increased life expectancy necessitates the need to understand the processes that underlie successful versus pathological brain ageing in order to develop early interventions which may assist in delaying if not reversing the detrimental effects of brain ageing. This review focuses on a signalling system of insulin and insulin-like growth factor IGF-1 (IIS) and its roles in cerebral ageing; it highlights some conflicting literature opinions and incomplete understanding of the roles and mechanisms of the IIS system.

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**INTRODUCTION**

Ageing is a complex biological process that affects all species ranging from invertebrates through to non-human mammals and humans, being underpinned by alterations at molecular and cellular levels[1,2]that compromise the organism’s physiological homeostasis, induce susceptibility to disease and accelerate death[3-5]. The cellular and anatomical changes that occur in the course of brain ageing contribute to cerebrovascular disease[6], impact motor performance and learning and memory functions[7,8], thus leading to cognitive decline and dementia[9]. As human life span is growing and the proportion of the elderly is increasing in most societies, the prevalence of age-dependent diseases such as Alzheimer’s (AD), Parkinson’s disease (PD) and stroke is also on the increase world-wide. Consequently, understanding the biological and molecular mechanisms of what constitutes ‘successful’ versus pathological cerebral ageing is critical to both delaying the ageing process, enhancing the quality of life in the elderly, and alleviating the already overburdened health care systems, from the cost component involved in treating age-related diseases.

In view of the above points, research on brain-ageing has generated a pool of information regarding the potential mechanisms, which underpin cognitive decline. Advancements in molecular and cell technology, have been instrumental in identifying factors such as oxidative stress[10,11], epigenetic changes[12], mitochondrial dysfunction, inflammatory response[13], impaired cell signalling and gene expressions[14], autophagy and protein turnover, target of rapamycin (TOR) and insulin/ insulin-like growth factor (IGF) signalling as potential mechanisms that contribute to alterations observed in brain ageing[9].

This review will first discuss what constitutes “successful” *vs* pathological brain ageing. Within this context, the review will then focus predominantly on the evolutionarily conserved insulin/IGF-signalling (IIS) system, and its roles in cognitive decline, dementia, Alzheimer’s disease and neuroinflammation.

It has been postulated that the IIS system plays a regulatory role in organismal ageing, lifespan and longevity[15,16]*,* and a reduced expression of its components under experimental conditions has been linked to amelioration of amyloid-β accumulation, the latter being one of the key features of Alzheimer’s disease[17-19], and cognitive impairment[20]. The IIS system merits an arduous and in depth investigation into the role and the extent of its involvement in cerebral aging, as targeting its components may pave the way to designing novel pharmacological approaches to early interventions and facilitate reversal or delay of cognitive decline in human patients.

**SUCCESSFUL VERSUS PATHOLOGICAL CEREBRAL AGEING**

Defining successful cerebral ageing has been both challenging and controversial and to date there is no scientific consensus defining normal ageing in older age. Despite the lack of an operational definition, it is generally agreed that successful cerebral ageing is a multi-dimensional process, characterized by the absence of cognitive impairment and preservation of mental faculties, which allows for social functioning and independence in older age[21]. This suggests that beyond the neurophysiological and psychological functions, equally vital are some esoteric elements such as wisdom and resilience, which together with lifestyle factors may contribute towards the variability, detected in cognitive abilities amongst “successful” versus “unsuccessful” elderly individuals and groups[22,23].

Current research postulates that the ageing mammalian brain retains a considerable functional plasticity, which is activity-related and thus it depends on the lifestyle of the individual (*e.g.,*[24]. There is evidence that human age-related diseases can be delayed by a healthy lifestyle which includes stress management, physical exercise and caloric restriction[24,25]. Thus, although genes are important determinants of longevity, an individual’s lifestyle is a powerful instrument that can delay the development of age-related diseases and lead to the path of ageing successfully[25-27].

Functional imaging studies on ageing human brains, suggest that in the absence of pathology, age-related cognitive decline is rather modest and varies amongst individuals[9]. It is characterized by anatomical and functional changes, which are associated with neuronal-synaptic molecular substrates specific to brain area[28,29]. These changes may be attributed to synaptic connectivity rather than neuronal and white matter loss[30,31].

In contrast, the pathologically ageing brain, as that in Alzheimer’s disease (AD), exhibits marked cognitive decline, which is associated with a significant loss of synapses[32]. Although the molecular mechanisms underlying this synaptic impairment are not fully understood, dysfunction of γ-secretase is evident in many cases of early onset of AD[33], and the gamma-secretase-mediated EphA4 signalling system may be involved in the synaptic pathogenesis of AD[32,33]. Equally, apolipoprotein E4 can increase the presence of amyloid beta (aβ) oligomers in the brain, which in turn may increase the loss of dendritic spines and accelerate memory decline in AD[34].

Of the regions associated with memory and learning, the hippocampal formation exhibit age-related decrease in volume, which may be a consequence of a decrease in neuronal and synaptic density[28,30]; prefrontal cortex (PFC) also shows reductions in grey matter[35,36]. The PFC is implicated in higher executive functions, involving explicit, implicit and spatial memories[28,37,38]. Its decreased grey matter diffusivity may be a potential biomarker for early AD[39].

Similarly, the posterior cingulate (PCC), which is both anatomically and functionally connected to PFC and the medial temporal lobe (MTL)[40,41] and which plays a vital role in encoding and retrieval of information[42,43] is also affected in ageing. Interestingly, it is one of the first structures to be affected in Alzheimer’s disease[44,45] but has not yet been explicitly studied in conjunction with PFC to establish associations between task-related and cognitive task activation[46].

These associations may be modifiable in healthily aged individuals[46-48] in contrast to AD patients[48-50]. PFC grey matter loss may trigger plasticity, which is dependent on the MTL function for memory tasks[51], and consequently, those individuals with functionally intact grey matter/MTL ratio, may make a greater use of the PFC[52].

The hippocampal region implicated in memory function shows an age-related atrophy[53], and a decline of working memory function is often observed in healthy ageing[54]. In AD pathology, impaired hippocampal function is detectable even before the formation and accumulation of plaques[55] and volume analysis by means of MRI has been used as diagnostic tool in distinguishing AD patients and healthy age-matched subjects by measuring the grey matter volumes in the lateral temporal and parietal cortices[56]. Furthermore, the AD brain is characterized by ventricular enlargement[57-60], consistent with a considerable loss of grey and white matter[61].

The above alterations may be attributed to age-related neuronal loss, and/or compensatory plasticity, and future studies are needed to test how these three way structure-function-behaviour associations impact the grey matter loss of PFC activation in successful ageing[46]. Equally, stress-related hormonal changes[9] or compromised calcium homeostasis[38,62] can play a role too as prolonged increases of intracellular calcium concentrations may cause neurite degeneration and cell death in ageing[63]*.*

In addition to the observed anatomical, functional and cellular changes, the brain’s neurochemistry is also affected, with dopaminergic, noradrenergic and cholinergic systems exhibiting deficits[60,64-69]. Studies on human and rhesus monkey PFC indicate that the balance between inhibitory and excitatory neurotransmission is decreased[70] as an effect of reduced gene expression, which may compromise neural activity resulting in excitotoxicity and neurodegenerative pathology. Positron emission tomography (PET) scans in ageing humans show a reduction in dopamine synthesis in the striatum, of relevance to frontal lobe cognitive function[71]*,* and a marked decrease in dopamine receptor binding within caudate and putamen nuclei[66,72].

Reductions in serotonin synthesis, reuptake and receptor binding have also been noted in the caudate nucleus, putamen and PFC of ageing brains[67], and glutamate decreased levels in grey and white matter, basal ganglia have been reported[69,73].

It is of significance that all the pathological features of AD such as neuronal loss, neurofibrillary tangles and plagues may be present in the brains of elderly who may never show the full extent of cognitive deterioration observed in AD[9]. This resilience to cognitive decline in the presence of AD pathology may be attributed to “cognitive reserve”, which may reduce the risk of dementia in ageing[74]. It further suggests that the hallmarks of AD may be secondary to ageing.

One of the cellular mechanisms regulating ageing processes is the insulin and insulin-like growth factor -1 signalling (IIS) system, which is described below with regard to its role and those of its components in cerebral ageing. This system, extensively studied in model organisms, appears to underpin the innate resilience that is essential in successful ageing; it may also present therapeutic potential in the treatment of debilitating neurodegenerative and cerebrovascular diseases.

**INSULIN, INSULIN GROWTH FACTORS AND THEIR RECEPTORS**

Insulin and the insulin-like growth factors 1 and 2 (IGF-1, IGF-2) constitute a family of structurally similar peptides[75,76], which have been preserved in most organisms through evolution[77]. Peripherally, insulin is synthesized and secreted into blood by pancreatic cells, whereas IGF-1 and IGF-2 by the liver in response to the pituitary growth hormone (GH)[78].

Insulin is a powerful player in glucose homeostasis, *e.g.,*[79,80], which targets the liver, muscle, and adipose tissue[81], and also the vasculature and the brain[82]. The IGF-1 in contrast, is implicated in foetal and postnatal development, with a role in cellular survival of adult tissues[82]. The circulation and delivery of IGF-1 to the tissues is aided by IGF-1 binding proteins (IGFBP1-6) in contrast to insulin, which circulates freely[82].

The transportation of insulin and IGF 1 into the brain is achieved through a saturable mechanism within the blood-brain barrier (BBB)[83,78,82], although there is evidence of their *de novo* synthesis in the CNS[84-86]*.* Insulin’s ability to cross the BBB[83,87-89] depends on a number of factors such as age, fasting or obesity[88]. Under experimental conditions, insulin administered directly into the CNS, decreases body weight by suppressing appetite, lowers serum insulin levels and increases serum glucose[90,91]. An increase in peripheral insulin levels leads to increased CSF insulin, whereas chronic insulin resistance impairs cerebral transportation by down regulating insulin receptors (IR) at BBB[92]. Brain activity in healthy individuals subjected to direct determination of insulin sensitivity with the hyperinsulinemic–euglycemic clamp technique, has been shown to be affected by increased levels of circulating insulin[93].

BBB uptake of IGF involves a lipoprotein receptor-related protein 1 (LRP1), the respective receptor (IGF-1R) and other transport mechanisms, enabling IGF access to CSF, and hypothalamic and hippocampal regions[82]. Insulin and IGFs activate signalling systems through their respective receptors, which belong to the tyrosine kinase receptor family[77]: insulin receptor (IR), IGF-1 receptor (IGF-1R**)** and IGF-2 receptor (IGF-2R) (Figure 1).Low affinity binding can take place between insulin and IGF-1R, and IGF-1 and IRusing the PI3K/Akt pathway**,** whileIGF-2 signals downstream not only via IGF-2R but also IGF-1R[77]. It should be mentioned that IGF-2R mainly controls the uptake and activation/destruction of extracellular of IGF-1/2 IGF2[94]; the present review is focused on IGF-1R (Figure 1).

IR and IGF-1Rdiffer in their respective functions and tissue expressions[82] being present in the brain within neuron rich structures[95-97] and glial cells[98,18,99]; they are different entities expressed in diverse brain regions. The IR ishighly expressed in the anterior thalamic and hypothalamic nuclei, olfactory bulb, hippocampus, cerebral cortex[100,101] and promotes plasticity through supporting synaptogenesis and synaptic remodelling[102,103], and metabolic homeostasis[75,104]. IGF-1R signalling supports normal brain development with its neurogenesis, and successful ageing, consistent with the roles of its agonist neurotrophins (see review[77]. A genetic modification, which results in IGF-1R deletion, causes microcephaly and death in experimental animals[105,106].

**INSULIN AND THE INSULIN-LIKE GROWTH FACTOR (IGF-1) SIGNALLING SYSTEM (IIS) AND ITS ROLES IN COGNITIVE FUNCTION, BRAIN AGEING AND LONGEVITY**

The IIS system has been probably the most widely studied conserved mechanism that extends lifespan in worms, flies and mammals[16], linking longevity and successful ageing across the species[107,108]. It has been suggested that although insulin does not directly influence cerebral glucose transport, it appears to influence regionally the distribution of glucose transporter isoforms such as GLUT 4 and GLUT 8; the former being expressed in the cerebellum, hippocampus, pituitary and hypothalamus[109] whereas the latter in the hippocampus and hypothalamus[110]. This selective stimulation of glucose uptake in the brain areas implicated in learning and memory renders the hormone a potent player in potential therapeutic use to restore or enhance impaired cognitive functions[111].In addition, insulin’s indirect role in hippocampal functioning via the long-term potentiation (LTP) cascade, involving the NMDA receptor[112] further suggests that insulin can be implicated in synaptic remodelling which is vital for the formation of new memories.

Similarly, insulin’s ability to modulate CNS levels of acetylcholine and norepinephrine, known to influence cognitive function[113,114], may further substantiate its role in neural activity and potential neural protection against the effects of oxidative stress[115].

Studies in animals and humans have suggested that deficiency or reduced effectiveness of insulin is a contributing factor to cognitive decline, impacting memory functions and brain ageing[116-118]. Insulin resistance has been positively correlated with neurodegeneration observed in AD and mild cognitive impairment[119,118]. Patients with type II diabetes mellitus, hypertension and chronic hyperinsulinemia show impaired verbal memory while enhanced memory function has been observed upon intranasal insulin administration[120,121].

In preclinical studies, LID mice, deficient in liver-derived IGF-1 exhibit impaired spatial learning and memory functions[122], demonstrating that this peptide is vital in mediating exercise-induced effects on the adult brain, thus suggesting promotion of neurogenesis[123,124]. In addition, IGF-1 appears to possess neurotrophic properties and plays a role in the amelioration of age-related reduction in hippocampal neurogenesis and behavioural deficits[125,126]*;* it also improves regional cerebral blood flow in normal rats[127]. It targets brain neurones and glia implying a trophic action on glutamatergic synapses, modulating hippocampal circuitries that are involved in learning and memory[116].

Within this context, research on brain ageing suggests that IGF-1 has potent effects on brain function, and that its reduced signalling during ageing may contribute to cognitive deterioration and compromise the organism’s ability to deal with age-associated cerebral pathologies[19]. Similarly, impaired insulin signalling in the brain has been linked to cognitive decline associated with pathological brain ageing[111,128]. Epidemiological studies suggest that individuals with type II diabetes and obesity may be at higher risk of developing vascular dementia[129].

On the other hand, centenarian studies provide evidence of correlation between reduced IIS activity and extreme human longevity. Ashkenazi centenarians have been found to have mutations in the IGF-1R that leads to lower activity of the respective signalling pathway[107], and centenarians' offspring had lower peripheral IGF-1 activity when compared with appropriately matched-controls[130]. Of significance, in the same sample of centenarians' offspring, IGF-1 was inversely related to insulin sensitivity[130], andan Italian cohort study reported an IR variant to be associated with longevity[131]. The abovefindings suggest that in humans the IIS system is acomplex determinant of lifespan[132].

**PRECLINICAL VERSUS CLINICAL STUDIES ON THE ROLE OF THE ISS SYSTEM IN ALZHEIMER’S DISEASE**

The importance of IR, IGF-1R and their respective agonist peptides has been underscored by data postulating its involvement in Alzheimer’s disease, which is characterized by amyloid-dependent neurodegeneration and late onset progressive cognitive decline. AD sufferers display impaired cerebral glucoregulation[133], reduced brain insulin receptor activity, reduced insulin concentrations in cerebrospinal fluid, peripheral hyperinsulinemia[134] and reduced insulin and IGF-1 expression[135], together with synaptic loss associated with the accumulation and formation of aggregate amyloid plagues (aβ) and neurofibrillary tangles (tau protein) as measured post mortem[136-138]. The above suggests that the IIS system may play a significant role in the loss of memory functions associated with AD and a reduction of its activity may reduced toxicity, delay amyloid-β accumulation and improve cognitive functions[139-143,18]*.*

In the preclinical approaches, mouse models of AD with a knockout of IGF-1 receptor exhibit reduced cognitive impairment, neurodegeneration and longer lifespan. The findings from the above studies, point to amyloid-β oligomers as the toxic species associated with AD, and the ageing process to be associated with the organism’s exposure to their toxicity, leading to age-related neurodegenerative diseases[132]. Consequently, the IIS system was mechanistically linked to neurone-associated toxic protein accumulation and ageing, as reduced signalling is thought to protect the brain and slow the progression of AD[132]. It has been shown to activate the P13K/AKT and RAS pathways (Figure 1). The former leads to the activation of mTOR (mammalian target of rapamycin), and rapamycin-treated mice have been shown to increase their lifespan and ameliorate age-related cognitive deficits[144,141]. The latter activates extracellular signal-regulated kinase (ERK-1/-2), which has been implicated in plasticity, including long-term potentiation, and memory formation in the CNS[145]. Although no data as yet exist to support the involvement of both pathways in the pathogenesis of AD, it may present an interesting direction for future research.

# A number of current preclinical studies on the animal models of AD suggest that genetic reduction of the signalling pathway may protect against the AD pathology[18,20] while older studies seem to postulate that its reduction is associated with the age-related pathologies[146]. These conflicting views may arise from the use of different experimental approaches[19], or as it has been suggested, reduced IGF-1 peripheral bioactivity may not necessarily induce the same results in brain IGF-1 levels[147], postulating an independent regulatory activity.

# It is important to appreciate the complexity of this relationship as human studies which try to correlate peripheral levels of IGF-1/2 with cognitive functioning in health and disease, report disparate finding, as illustrated below. Of the most recent publications in this area, a large scale long-term study on a community sample of over 3500 participants of middle and old ages has demonstrated that lower serum levels of IGF-1 associate with an increased risk of developing AD dementia while higher levels of IGF-1 associate with greater brain volumes in middle-aged participants free of stroke and dementia. The authors conclude that elevated levels of IGF-1 may protect against neurodegeneration[148]. On the other hand, the Caerphilly Prospective Study on 746 men has not found associations between age-related cognitive decline and IGF-1, contrary to IGF-2 which was associated with both normal age-related and pathological cognitive decline[149]. Furthermore, offspring from families with a parental history of AD appear to have higher serum IGF-1 levels in middle age when compared with appropriate controls, leading to a conclusion that elevated peripheral IGF-1 associates with an increased risk of AD[150].

Despite the existence of opposing views in the field, epidemiological evidence postulates a strong association between T2D and AD occurrence as AD patients exhibit higher rates of diabetes and impaired fasting glucose levels[151-153], and although the molecular mechanisms underlying this association are not yet clearly understood[82] impaired insulin signalling, amyloid-genesis and inflammation appear to be heavily implicated in the aetiology of diabetes, AD and consequently cerebral ageing[154].

**IIS SYSTEM AND INFLAMMATION**

Inflammation is seen a key player in obesity, insulin resistance and diabetes, as based on elevated levels of pro-inflammatory cytokines in the circulation and pancreatic islets of T2D patients[155]. Similarly, elevated levels of pro-inflammatory proteins and chemokines have been detected in post-mortem AD patients’ brains, *e.g.,*[156]. This was further substantiated by findings from studies on AD mouse models suggestive of inflammation as key to early and/or intermediate stages of the neurodegenerative condition[157]. There is consensus that cerebrovascular inflammation and neuroinflammation, along with an increased accumulation of toxic amyloid- β, all result in a disruption of synaptic activity, which according to some theories is a trigger in AD pathophysiology, *e.g.,*[158].

Studies investigating IGF-1 and IGF-2 peptides’ expression in human microglia *in vivo* and *in vitro* suggest that both peptides are expressed in microglia, conferring vital protection against cytokine-mediated neuronal death. It should be mentioned here that microglial activation is associated with increased activities of inflammatory cytokines, *e.g.,* IL-1β and IL-6 which itself can disrupt neural signalling, *e.g.,*[159].

Chronic inflammation increases the production of inflammatory cytokines in the long-term, which contributes to the suppression of neurotrophic factors, including the IGFs, and leads to progressive tissue damage, thus accelerating the onset of clinical manifestations of AD and metabolic disorders including T2D[160,161], and may contribute to neurodegeneration[162].

**CONCLUSION**

Research on brain ageing suggests that age itself is a major risk factor for the development of age-related cognitive decline, Alzheimer’s and cerebrovascular diseases. The increased life expectancy observed in most societies has further necessitated the need to understand the processes that underlie successful versus pathological brain ageing such that early interventions through lifestyle modifications or pharmacological agents may assist in delaying if not reversing the detrimental effects on brain pathology.

Within this context, this review examined the role of an evolutionarily conserved signalling pathway, IIS, with the focus on insulin and insulin-like growth factor IGF-1 and their roles in cerebral ageing. Translation of data derived from animal models allow for linking the IIS pathway with its supporting longevity, protein homeostasis, learning and memory, and delayed ageing. The above is also consistent with the human studies, which find evidence of reduced messaging for insulin, IGF-1 and their receptors in post mortem brains of patients with AD. While the link between insulin as such and brain ageing has been recognised, the IIS pathway in its entirety deserves more attention; our still incomplete understanding of the roles and mechanisms of this pathway calls for more translational research to explore novel treatments for cognitive decline through delaying cerebral ageing.

Some conflicting literature opinions and incomplete understanding of the roles and mechanisms of the IIS system demand novel approaches and directions in this field. The IIS system clearly lends itself to the ongoing search for modifiable physiological factors which may delay the onset of cognitive decline and cerebral ageing.

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**Figure 1 Insulin and insulin-like growth factor signalling pathways-a simplified outline[77].** Low affinity binding between insulin and IGF-1R, and IGF-1 and IR**,** and IGF-2 and IR is represented by dashed lines.Ach: Acetylcholine; ERK: RAS-extracellular signal-related kinase; GRB: Growth factor receptor-bound protein**;** IGF-1: Insulin-like growth factor 1; IGF-2: Insulin-like growth factor 2; IR: Insulin receptor; IGF-1R: IGF-1 receptor; IGF-2R: IGF-2 receptor; Mtor: Mammalian target of rapamycin; PLC：Phospholipase C; PKC: Protein kinase C; PI3K: Phosphoinositide 3-kinase.

