THEMATIC REVIEW

40 YEARS of IGF1

IGF1: the Jekyll and Hyde of the aging brain

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Abstract

The insulin-like growth factor 1 (IGF1) signaling pathway has emerged as a major regulator of the aging process, from rodents to humans. However, given the pleiotropic actions of IGF1, its role in the aging brain remains complex and controversial. While IGF1 is clearly essential for normal development of the central nervous system, conflicting evidence has emerged from preclinical and human studies regarding its relationship to cognitive function, as well as cerebrovascular and neurodegenerative disorders. This review delves into the current state of the evidence examining the role of IGF1 in the aging brain, encompassing preclinical and clinical studies. A broad examination of the data indicates that IGF1 may indeed play opposing roles in the aging brain, depending on the underlying pathology and context. Some evidence suggests that in the setting of neurodegenerative diseases that manifest with abnormal protein deposition in the brain, such as Alzheimer's disease, reducing IGF1 signaling may serve a protective role by slowing disease progression and augmenting clearance of pathologic proteins to maintain cellular homeostasis. In contrast, inducing IGF1 deficiency has also been implicated in dysregulated function of cognition and the neurovascular system, suggesting that some IGF1 signaling may be necessary for normal brain function. Furthermore, states of acute neuronal injury, which necessitate growth, repair and survival signals to persevere, typically demonstrate salutary effects of IGF1 in that context. Appreciating the dual, at times opposing 'Dr Jekyll' and 'Mr Hyde' characteristics of IGF1 in the aging brain, will bring us closer to understanding its impact and devising more targeted IGF1-related interventions.

Key Words
- Alzheimer's
- cognition
- Parkinson's
- CNS

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Introduction

The growth hormone/insulin-like growth factor 1 (GH/IGF1) signaling pathway, also referred to as the somatotropic axis, has been extensively implicated in the aging process (Bartke *et al.* 2003, Kenyon 2010, Barzilai *et al.* 2012, Brown-Borg & Bartke 2012). Attenuation of this conserved signaling pathway has been demonstrated to reduce the incidence of age-related diseases and extend survival in numerous rodent models (Brown-Borg *et al.* 1996, Kinney

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et al. 2001*a*,*b*, Ikeno *et al.* 2003). Remarkably, this pathway also appears to be relevant to human aging, as functional mutations in the *IGF1R* resulting in attenuated IGF1 signaling are enriched in centenarians (Suh *et al.* 2008, Tazearslan *et al.* 2011), while stratifying nonagenarian females by IGF1 levels revealed a survival advantage in those with low IGF1 (Milman *et al.* 2014). Likewise, lower serum IGF1 levels were associated with protection from cognitive impairment late into the tenth decade among women (Perice *et al.* 2016). The role of IGF1 in the central nervous system (CNS) has been a particularly intriguing, albeit controversial area of investigation, with evidence linking IGF1 to favorable, detrimental and indifferent effects on CNS function and disease risk. In this review, we will delve into the current state of the evidence examining the role of IGF1 in the aging brain, with a particular focus on the consistencies and controversies that have emerged from preclinical and clinical studies.

IGF1 and the brain

Endocrine vs autocrine IGF1

Similar to many other tissues, the brain is exposed to two sources of IGF1, endocrine and autocrine. The regulation of endocrine production of IGF1, which is primarily under the control of GH pulses secreted from the pituitary in response to GH-releasing hormone (GHRH) and ghrelin, consists of a classic negative feedback loop and has been extensively described elsewhere (Berelowitz *et al.* 1981). In brief, GH binds to the GH receptor to stimulate IGF1 production mainly in the liver and the rise in circulating IGF1 levels results in enhanced binding to IGF1 receptors (IGF1R) in the pituitary and the hypothalamus to inhibit GH and GHRH secretion, respectively. Hepatic-derived IGF1 comprises ~70% of total circulating IGF1 (Ohlsson *et al.* 2009) levels and can provide input to the CNS by crossing the blood–brain barrier (BBB) at the choroid plexus into the cerebrospinal fluid (CSF) via the IGF1R and low-density lipoprotein receptor-related protein 2 transport protein (also known as megalin) (Carro *et al.* 2005). During early life, IGF1 is abundantly expressed throughout the CNS and is essential for normal brain development. The critical role of autocrine IGF1 for neuronal development is evidenced by findings that mutations resulting in global IGF1 loss or insensitivity manifest as microcephaly and cognitive deficiencies in children (Woods *et al.* 1996, Abuzzahab *et al.* 2003, Netchine *et al.* 2011). In contrast, mutations that result in GH deficiency or resistance frequently present with normal cognitive ability (Kranzler *et al.* 1998) suggesting that autocrine brain IGF1 production may be preserved in these individuals (Joseph D'Ercole & Ye 2008). In the circulation, most IGF1 is bound to IGF-binding proteins (IGFBP), with IGFBP-3 being most abundant, and therefore, is inactive (Rajaram *et al.* 1997, Baxter 2000, Holly & Perks 2012). IGF1 exerts its action in tissues by binding to the high-affinity IGF1R on the cell surface (Holly & Perks 2012); notably, IGF1 also binds to the insulin receptor, but with much lower affinity (Novosyadlyy & Leroith 2012). IGF1 binding to the IGF1R initiates a complex intracellular signaling cascade that includes phosphorylation of the insulin receptor substrate (IRS) molecules and subsequent activation of phosphoinositide 3-kinase-protein kinase B (PI3K-Akt) and the the mitogen-activated protein kinase (MAPK) pathways that regulate, among several downstream effectors, mechanistic target of rapamycin (mTOR) activity and Forkhead box O translocation (FOXO) (Taniguchi *et al.* 2006). Signaling through these pathways influences autophagy, growth, stress resistance, oxidative stress and lifespan (Barzilai *et al.* 2012).

IGF1 and the aging brain

In the brain, autocrine IGF1 production is thought to peak during development (Joseph D'Ercole & Ye 2008). Meanwhile, endocrine production of IGF1, and presumably IGF1 input into the CNS, remains high during the early years, peaking during puberty, a period that coincides with rapid cell proliferation and linear growth (Yamamoto *et al.* 1991). By the third decade, IGF1 production abruptly drops off and then continues steadily declining with aging, raising questions regarding the potential role of reduced IGF1 levels in the manifestations of brain aging (Yamamoto *et al.* 1991). The endocrine decline in IGF1 has been attributed to diminished GH pulse amplitude and frequency that is observed in aging, at least in part due to decreased ghrelin binding to the GH secretagogue receptor (GHSR) (Sun *et al.* 2004), thus resulting in steady, but low-level secretion of GH in older individuals (Carlson *et al.* 1972, Finkelstein *et al.* 1972). Limited evidence suggests that concomitant with the decline in systemic IGF1 levels, local production, as assessed by CSF and brain tissues levels, also declines with age, in spite of the fact that brain IGF1 production is believed to act independent of GH regulation (Ashpole *et al.* 2015). In fact, observations from aged rodent models show that IGF1R transcription increases with age in the hippocampal and cortical regions of the brain, possibly in a compensatory attempt to preserve brain IGF1 signaling in the setting of less IGF1 availability; however, this response is inadequate

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to restore IGF1 back to youthful levels and IGF1 levels in the brain of aged animals remain lower compared to young animals (Ashpole *et al.* 2015). Beyond the decline in local and systemic IGF1 levels with aging, there is some evidence that the aged brain may be resistant to IGF1 signaling (Muller *et al.* 2012). Observations of declining autocrine and endocrine IGF1 levels with age, paired with knowledge that aging is associated with increased risk of cognitive decline and diseases affecting the brain, beg the question of whether IGF1 is involved in brain aging.

IGF1 and cognition

Epidemiologic and clinical studies

Age-related cognitive decline, which in its more progressive forms, may be characterized by mild cognitive impairment (MCI) or dementia, secondary to causes such as cerebrovascular ischemia or Alzheimer's disease (AD), poses a significant burden for an increasingly aging population, raising the urgency to identify underlying contributors to these conditions in order to delay or prevent their onset (Prince *et al.* 2016, Langa *et al.* 2017, Wu *et al.* 2017). Studies in humans and rodents have been conducted into the possible relationship between IGF1 and the cognitive domain, and have uncovered interesting, albeit at times conflicting associations (Frater *et al.* 2017). A number of cross-sectional studies in middle and older age adults have revealed a positive correlation between IGF1 levels and cognition (Al-Delaimy *et al.* 2009, Doi *et al.* 2015, Wennberg *et al.* 2018). However, this observation was not always consistent between sexes, with significant findings limited only to males or females across different studies (Al-Delaimy *et al.* 2009, Wennberg *et al.* 2018). On the other hand, another cross-sectional analysis found an inverse relationship between IGF1 and cognitive processing capacity in men age 60 years and older (Tumati *et al.* 2016). Likewise, in a cohort of exceptional longevity, females with IGF1 levels in the lowest tertile had a nearly 50% lower prevalence of cognitive impairment compared to females with IGF1 levels in the upper two tertiles (Perice *et al.* 2016). Similarly, prospective studies have done little to settle this controversy. One study demonstrated a positive association between baseline serum IGF1 levels and future cognitive performance among older women (Okereke *et al.* 2007), whereas another found no association in men (Green *et al.* 2014). Yet, a different prospective analysis found lower cognitive scores among men with highest baseline IGF1 levels after 8 years of follow-up (Tumati *et al.* 2016). Higher serum IGF1 levels were also correlated with greater total brain volume on MRI in older and middle-aged adults without dementia, but no relationship with hippocampal volume was noted (Westwood *et al.* 2014). Clinical trials have further fueled the uncertainty regarding the role of IGF1 on cognition. A 20-week intervention study showed beneficial effects of GHRH administration on cognitive function in older adults who were healthy or had MCI (Baker *et al.* 2012). However, a year-long experimental replacement of peripheral IGF1 in older females failed to achieve discernible benefits in cognitive outcomes (Friedlander *et al.* 2001). Although the results from human studies do not offer a conclusive resolution about the role of IGF1 on cognitive function in aging, they should be interpreted in the context of substantial heterogeneity between cohorts, cognitive assessment tools and definitions of cognitive function. Extended longitudinal follow-up paired with more precise characterization may help clarify this uncertainly in the future.

Molecular and animal studies

In rodents, few studies have been conducted that address cognition in the context of aging. However, one study exploring the potential therapeutic benefit of administering IGF1 by intracerebroventricular (ICV) infusion to old male Fisher-Brown Norway (FBN) rats over a 1 month period demonstrated improved cognitive function, in terms of spatial reference memory and working memory (Markowska *et al.* 1998, Pardo *et al.* 2018). It has also been shown that old male FBN rats have a decreased number of newly generated cells in the hippocampus, a brain region important for memory domain acquisition, as well as a significant reduction of newborn cells differentiating into neurons (Lichtenwalner *et al.* 2001). However, ICV administration of IGF1 significantly restored hippocampal neurogenesis, without an effect on progenitor differentiation or newborn cell survival, which could be related to the observed improvement in cognitive function noted previously in this strain of rats (Lichtenwalner *et al.* 2001). Furthermore, old female Sprague–Dawley rats injected ICV with an IGF1-expressing adenovirus resulted in increased IGF1 levels in CSF, and restoration of neurogenesis and spatial memory assessed by the Barnes maze (Pardo *et al.* 2016, 2018). In this model, transcription of genes related to synaptic function and neurogenesis was upregulated (Pardo *et al.* 2018). Astrocyte-specific knockout of *Igf1r* gene at 3–4 months of age resulted in impairments in working memory in mice; however, it is not known what effect

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this intervention may have at an older age (Logan *et al.* 2018). Interestingly, both male and female long-lived Ames dwarf mice, which are characterized by circulating GH and IGF1 deficiency, have normal cognitive function that is better maintained with age, based on performance in memory tests, when compared to age-matched controls (Kinney *et al.* 2001*b*). Although there is some evidence that local IGF1 production in these animals is enhanced (Sun *et al.* 2005), suggesting that autocrine IGF1 production may be an important contributor to cognitive health, subsequent studies did not confirm these results, finding lower IGF1 levels in the cortex and hippocampus of these mice compared to wild-type controls (Puig *et al.* 2016). On the contrary, liver-specific IGF1-deficient mice, which have an approximately 70% reduction in systemic IGF1 levels, manifest early hippocampal-dependent cognitive deficits (Trejo *et al.* 2007), including a reduction in spatial learning and memory (assessed by Water Maze) (Svensson *et al.* 2006, Trejo *et al.* 2007) despite maintained autocrine IGF1 production. However, these mice also present with markedly elevated GH levels, due to lack of feedback inhibition by IGF1, resulting in insulin resistance (Haluzik *et al.* 2003), and these perturbations in GH and insulin may also directly contribute to the neuronal and vascular dysfunction observed in this model (Bailey-Downs *et al.* 2012, Talbot *et al.* 2012).

IGF1 and AD

Epidemiologic and clinical studies

AD, characterized by a progressive decline in memory and loss of independent functioning, has become a major burden for older adults, their families and the health care system (Callahan 2017). Although IGF1 has been extensively investigated in AD patients, most of the studies have been observational and substantial controversy continues to surround this topic in epidemiologic literature. A meta-analysis of nine case–control studies did not find an association between IGF1 levels and AD, with individual studies showing higher, similar and lower serum IGF1 levels in AD patients compared to controls (Ostrowski *et al.* 2016). On the other hand, a prospective study demonstrated an inverse association between baseline serum IGF1 levels and AD risk (Westwood *et al.* 2014), while an analysis of AD patients reported that lower baseline serum IGF1 was associated with faster progression in cognitive decline over 2 years (Vidal *et al.* 2016). Additionally, a clinical trial that evaluated the effect of a GH secretagogue on progression of AD revealed a lack of efficacy, despite achieving higher IGF1 levels (Sevigny *et al.* 2008). Interestingly, higher measured stimulating activity of the IGF1R using a specialized assay was related to greater prevalence and incidence of dementia (de Bruijn *et al.* 2014). Acknowledging that IGF1 bioavailability is tightly regulated by IGFBPs and that genetic or acquired conditions may predispose to IGF1 resistance (Suh *et al.* 2008, Tazearslan *et al.* 2011), this latter study raises the important consideration that IGF1 levels may not always be indicative of action, especially in aging and diseased brains, where IGF1 resistance has been reported to occur (Muller *et al.* 2012, Talbot *et al.* 2012).

Molecular and animal studies

Molecular and animal studies attempting to shed light on the role of somatotropic signaling in AD have also not been free of controversy. A number of rodent studies have suggested that relative IGF1 deficiency and/or reduced IGF1 signaling confers protection against progression of AD pathology. For instance, Ames Dwarf mice expressing human mutant amyloid precursor protein (APP) and presenillin-1 (PS1) demonstrated lower brain IGF1 levels and reduced amyloid plaque deposition than controls (Puig *et al.* 2016). Likewise, heterozygous deletion of the *Igf1r* in a similar AD model protected from AD-like symptoms, neuroinflammation, neuronal loss and delayed proteotoxicity in 12-to 13-month-old mice compared to age-matched controls (Cohen *et al.* 2009). Deletion of neuronal *Igf1r* or *Irs2*, which signals downstream of IGF1R, demonstrated reduced amyloid plaque accumulation, reduced neuroinflammation, improved spatial memory and delayed death in APP and APP/PS1 models (Freude *et al.* 2009, Gontier *et al.* 2015). However, there was no benefit to reducing IGF1 signaling in an advanced model of AD (George *et al.* 2017), suggesting that there may be a limited window for intervention. Adult-onset deletion of *IGF1R* specifically in neurons also reduced neuronal size through changes to the soma and dendrites (Gontier *et al.* 2015, George *et al.* 2017), suggesting that larger volume does not necessarily equate with better function (Westwood *et al.* 2014). Of note, subjecting 3×Tg-AD mice to protein restriction cycles, which reduces circulating IGF1 levels by 30–70% (Parrella *et al.* 2013), alleviated symptoms of working memory and short-term spatial memory deficits, as well as reduced hippocampal Tau phosphorylation (Parrella *et al.* 2013) that is associated with cognitive deficits in humans with AD (de Leon *et al.* 2006). In contrast to evidence implicating IGF1 as a detrimental player in AD pathology, age-related decline

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in IGF1 has been linked with brain metabolic deficiencies in AD mouse models (Carro *et al.* 2002, Trueba-Saiz *et al.* 2013) and treatment with IGF1 has been shown to confer protection in hippocampal neurons from the toxic effects of amyloid peptides (Dore *et al.* 1997). However, results that showed that peripheral administration of IGF1 promoted clearance of Aβ amyloid in aged rats and mutant mice (Carro *et al.* 2002, 2006) have not been replicated in later studies (Lanz *et al.* 2008).

Interestingly, a study in human AD brains documented insulin and IGF1 resistance via decreased activation of downstream signaling of IRS-1 and IGF1R/IRS-2, respectively (Talbot *et al.* 2012). Similar findings have been observed in rodent models (Muller *et al.* 2012, Trueba-Saiz *et al.* 2013). Whether brain resistance to IGF1 is a pathologic feature or a protective adaption remains uncertain. However, a recent genome-wide microarray analysis that compared neurons in early-stage AD with *IGF1R*-knockout neurons demonstrated very similar transcriptomic signatures, suggesting that IGF1 resistance in AD neurons may be an adaptive response intended to protect neurons from further damage (George *et al.* 2017). In contrast, several investigators have proposed that reduced CNS input of a related hormone, insulin, may underlie cognitive impairment, and data have demonstrated that intranasal delivery of insulin improves cognition in individuals with MCI or early-stage AD (Claxton *et al.* 2015). While this latter observation seems somewhat contradictory to those results obtained from AD models, it is important to note that data from the intervention trial were obtained from individuals with MCI or early-stage disease. Therefore, the relationship of insulin and IGF1 signaling to cognition could vary based upon disease susceptibility and severity, a possibility that will require further study to confirm.

Mechanistically, many potential pathways and processes are impacted by IGF1, which could have both beneficial and detrimental effects on the CNS to influence brain aging, cognitive decline and AD. Certainly, IGF1 has been linked to neurogenesis, axonal and dendrite growth, synaptogenesis, myelination and neuronal cell survival (Liang *et al.* 2007, Nieto-Estevez *et al.* 2016). On the other hand, increased IGF1 signaling could impair macroautophagy in neurons, which is a cellular process shown to confer protection from AD. Macroautophagy is the process that eliminates cellular components through sequestration in autophagosomes followed by degradation upon fusion with lysosomes and plays an important role in eliminating misfolded or aggregated proteins that can be damaging to cells. This process has been shown to be dysfunctional not only in aging, but also in age-related neurodegenerative diseases that include Parkinson's disease (PD), as well as sporadic and familial AD (Martinez-Vicente & Cuervo 2007, Lee *et al.* 2010). Indeed, reduced somatotropic signaling has been implicated in increased macroautophagy. In nematodes, loss of IGF1 signaling was associated with improved autophagy, a pathway required for lifespan extension observed in this model (Melendez *et al.* 2003). Knockout of *IGF1R* in neurons resulted in better autophagy and clearance of Aβ plaques (Gontier *et al.* 2015), whereas prolonged exposure to IGF1 resulted in decreased autophagy in human fibroblasts (Bitto *et al.* 2010). Autophagy was also induced by inhibition of mTOR or AMPK, molecules that signal downstream of IGF1R (Samari & Seglen 1998, Schmelzle & Hall 2000). In summary, most of the experimental evidence suggests that IGF1 acts as 'Mr. Hyde' in the progression of AD. However, what character IGF1 signaling plays preceding disease onset remains to be definitively determined.

IGF1 and PD

Epidemiologic and clinical studies

PD is a progressive neurodegenerative disorder distinctively characterized clinically by rest tremor, rigidity and bradykinesia, and pathologically by the destruction of dopaminergic (DA) neurons in the substantia nigra (SN) (Forno 1996) in the basal ganglia. However, PD is often accompanied by several other cognitive and neuropsychiatric dysfunctions, as well as accumulation of Lewy bodies throughout the brain, that include alpha-synuclein among other proteins, suggesting that the neurodegenerative process also targets other brain areas (Mu *et al.* 2017, Schapira *et al.* 2017). Circulating IGF1 has been proposed as a potential biomarker for PD. Significantly sustained elevations of IGF1 levels, without concomitant elevations in GH levels, were noted among patients with drug-treated, stable PD compared to healthy controls (Godau *et al.* 2010). Similarly, a small group of drug-naïve patients demonstrated elevations in serum IGF1 levels compared to controls (Godau *et al.* 2011). Higher IGF1 levels were also found among individuals with shorter duration of PD, with levels falling with longer disease duration (Numao *et al.* 2014), sometimes even reaching near-control levels (Godau *et al.* 2010). This was confirmed by other studies that noted that elevations in IGF1, GH and IGFBP-3 were less pronounced among patients with longer disease duration and more advanced PD (Tuncel *et al.* 2009). Interestingly, even individuals

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who did not meet criteria for PD diagnosis, but with some movement impairment and SN abnormalities on transcranial ultrasound, had higher IGF1 levels compared to controls without any abnormalities (Godau *et al*. 2011), suggesting that elevated IGF1 may be a potential risk factor for progression to PD. Indeed, a prospective study that followed early-stage PD patients for up to 2 years found that individuals with baseline IGF1 levels in the top quartile demonstrated worse motor impairment and Parkinsonian symptoms throughout the duration of the study, compared to those with baseline IGF1 in the lower quartiles (Picillo *et al*. 2013), with a caveat that the symptoms had not significantly progressed in either group due to effective medical treatment. It was also noted that patients with PD did not only manifest elevations in serum IGF1 and IGFBP levels compared to controls, but also had elevated levels of these proteins in the CSF (Mashayekhi *et al*. 2010), suggesting that circulating IGF1 crosses the BBB in PD. However, it still remains unresolved whether PD is associated with elevations of systemic or autocrine IGF1 levels, or both.

Serum IGF1 levels have also been studied in association with other symptoms of PD. Patients with PD have an approximate 6-fold increased risk for developing dementia, compared to the general population (Aarsland *et al*. 2001). In contrast to those reports described earlier, PD patients with higher baseline IGF1 levels demonstrated better attention and executive functions after 2 years of follow-up (Pellecchia *et al*. 2014). In addition, a recent study of a large cohort of early, drug-naïve PD patients found worse executive function, attention and verbal memory among individuals with IGF1 levels in the lowest quartile (Picillo *et al*. 2017). These observations may indicate that higher IGF1 levels are in fact protective against PD-associated cognitive decline, although reverse causality cannot be ruled out, such that patients with lower IGF1 may actually have more advanced and sustained PD that is associated with more severe cognitive impairments, as suggested by studies above.

Molecular and animal studies

Some of the earlier evidence suggesting the relevance of IGF1 to DA neurons and PD was derived from autoradiographic studies demonstrating the presence of IGF1R in moderate densities in the SN of middle and older age adults (De Keyser *et al*. 1994). Experiments involving human and animal cell cultures have demonstrated neuroprotective actions of IGF1 on DA neurons (Zawada *et al*. 1996, Offen *et al*. 2001, Sun *et al*. 2010). Treatment of cell cultures obtained from E15 rat ventral mesencephalon with IGF1 resulted in a two-fold increased preservation the number of DA neurons. Follow-up studies further demonstrated that administration of IGF1 to rat cerebellar granular neurons increased protein expression of B-cell lymphoma-2 (*Bcl-2*), placing this potent cell survival factor downstream of IGF1 signaling to provide protection against DA apoptosis (Offen *et al*. 2001).

The role of IGF1 signaling has also been investigated in several models of PD. One such model uses 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a prodrug to the neurotoxin 1-methyl-4-phenyl pyridinium, to induce DA cell injury that is characteristic of PD. MPTP intoxication resulted in upregulated IGF1R levels that was not accompanied by changes in Akt phosphorylation levels (D'Astous *et al*. 2006). Using the same PD model, a different study found that intraperitoneal injection of MPTP resulted in more severe lesions in *Igf1r* haploinsufficient mice, as compared to controls (Nadjar *et al*. 2009), and further suggested that IGF1 signaling may oppose the anti-inflammatory and pro-oxidative effects provoked by this insult (Nadjar *et al*. 2009). Another PD model utilizing 6-hydroxydopamine induced unilateral nigrostriatal lesions in rats and also showed reduced neuronal loss and sustained motor function with peripherally or centrally administered IGF1 (Quesada & Micevych 2004). Interestingly, in this study, peripherally administered estrogen was also protective, but an IGF1R antagonist blocked the neuroprotective effects of both estrogen and IGF1, suggesting that the neuroprotective effect of estrogen may be mediated via IGF1 signaling.

In summary, both central and peripheral administrations of IGF1 have resulted in neuroprotection in animal PD models. However, it is important to note that the above referenced studies used PD models that introduced SN lesions using acute injury strategies, which is distinct from the etiology of the human disease that is characterized by slow, progressive neurodegenerative changes accompanied by abnormal deposition of proteins, such as alpha-synuclein. For instance, in *Drosophila* and *Caenorhabditis elegans*, reduced IGF1/insulin-like signaling (IIS) resulted in reduced neurotoxicity and alpha-synuclein misfolding, a feature of PD (Knight *et al*. 2014). Additionally, impaired autophagic function, a process that is inhibited by IGF1, has been implicated in PD pathogenesis (Menzies *et al*. 2017). Thus, the role of IGF1 needs to be further investigated in PD models that better represent the human disease.

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IGF1 and cerebrovascular disease

Epidemiologic and clinical studies

Whether circulating levels of IGF1 are associated with the risk of cerebrovascular events remains somewhat equivocal. A recent prospective study of older adults from the Framingham cohort demonstrated a 2.3-fold increase in incident stroke among individuals with baseline IGF1 in the lowest quintile (Saber *et al*. 2017). Free IGF1 was also inversely related to carotid artery intima-media thickness (Schwab *et al*. 1997, Van den Beld *et al*. 2003); however, no association was identified between IGF1, IGFBP-3 and IGF1:IGFBP-3 molar ratios and the risk of stroke among older participants in the Cardiovascular Health Study (Kaplan *et al*. 2007). On the other hand, a nested case–control analysis found an increase in stroke risk among individuals in the bottom quartile IGFBP-3, but the association between IGF1 and stroke was non-significant after adjustment for IGFBP-3 levels (Johnsen *et al*. 2005).

A number of studies have investigated IGF1 levels in patients who sustained strokes and its prognostic role in neurologic outcomes. One of the earlier studies found that levels of IGF1 and IGFBP-3 were lower in patients within 24 h of an acute ischemic stroke, as compared to age-matched subjects with non-ischemic neurological illness, and this difference persisted for at least 10 days after the event (Schwab *et al*. 1997). Several other studies similarly found reduced serum IGF1 and IGFBP-3 levels in patients with acute ischemic (Denti *et al*. 2004) and hemorrhagic strokes (Iso *et al*. 2012), while post-stroke serum IGF1 and IGFBP-3 levels were also inversely associated with infarct volume (Schwab *et al*. 1997, Tang *et al*. 2014). However, not all results have been consistent. One study described higher IGF1 levels within the first 10 days of ischemic stroke that remained elevated 3 months out from the event (Åberg *et al*. 2011). Another study did not find an association between IGF1 levels obtained within 6 h of stroke onset and stroke severity (De Smedt *et al*. 2011). However, in the same study, higher IGF1 levels during the acute stroke period and during the rehabilitation period were associated with better cognitive and functional recovery after the stroke. Åberg *et al*. showed that higher IGF1 levels acutely and at 3 months post stroke positively correlated with better functional recovery between 3 and 24 months (Åberg *et al*. 2011). Higher serum IGF1 levels among individuals during their rehabilitation after stroke were associated with better cognitive and functional recovery (Bondanelli *et al*. 2006). On the other hand, lower serum IGF1 levels on admission have been associated with unfavorable functional outcomes following acute ischemic stroke (Klionsky *et al*. 2016). Similarly, serum samples obtained from individuals with persistent chronic hemiparesis of ≥6 months duration showed lower IGF1 and IGFBP-3 serum levels (Silva-Couto *et al*. 2014).

In addition to functional outcomes, IGF1 levels have been investigated in relationship to survival and hospital discharge after a cerebrovascular event. Lower IGF1 serum levels have been associated with death at 90 days following ischemic stroke (Tang *et al*. 2014). IGF1 level of less than 60 ng/mL measured 24 h after an ischemic stroke was associated with higher 6-month mortality, but not with the severity of neurologic impairment (Denti *et al*. 2004); yet, the studied cohort was substantially older, therefore, the low IGF1, as well as the high mortality may have been attributable to older age. In contrast, another report found reduced serum IGF1 levels and IGF1/IGFBP ratios measured within 72 h and at 1 week following a stroke to be associated with a shorter hospital length of stay. However, patients with higher serum IGF1 had larger infarcts, and the higher levels may have been reflective of a more robust compensatory protective response (Mattlage *et al*. 2016).

Molecular and animal studies

In the setting of ischemic neural injury, IGF1 has been demonstrated to have neurotropic and neuroprotective activities (Knusel *et al*. 1990, Gluckman *et al*. 1992, Chung *et al*. 2007, Hu *et al*. 2009). Circulating IGF1 that can cross the BBB (De Geyter *et al*. 2016) and local IGF1 that is produced by proliferating microglia have been implicated in promoting neurological recovery after a stroke (Ploughman *et al*. 2005, Lalancette-Hébert *et al*. 2007, Thored *et al*. 2009). Following a middle cerebral artery occlusion (MCAO) in rats, IGF1 expression was found to be upregulated in the astrocytes surrounding the ischemic penumbra and neuronal progenitors (Yan *et al*. 2006), whereas the administration of an IGF1-neutralizing antibody significantly reduced progenitor proliferation, suggesting that IGF1 may be an important growth factor for neuronal recovery after a stroke. Evidence also indicates that neurological and functional recovery in the context of physical therapy is associated with marked activation of IGF1 and downstream Akt signaling in the peri-infarct region (Zheng *et al*. 2014). On the other hand, higher serum IGF1 levels prior to MCAO procedure in mice correlated with a larger infarct size (Endres *et al*. 2007).

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Impaired cerebrovascular function has also been demonstrated in several GH and/or IGF1 deficient models. One such model is the Lewis dwarf rat, which has a genetic GH deficiency that, among other outcomes, results in an increased incidence of late-life stroke (Sonntag *et al*. 2005). Similarly, studies in a mouse model of post-developmental liver knockdown of *Igf1* show that IGF1 deficiency has a negative effect on cerebrovascular adaptation to hypertension, and this dysfunction is most likely associated with BBB disruption, as well as neuroinflammation, mimicking the aging phenotype (Toth *et al*. 2014). Moreover, neurovascular coupling, which is a process that adjusts local cerebral blood flow to the energy requirements of activated neurons, is known to decrease with age (Toth *et al*. 2015). Using the same IGF1-deficient mouse model, Toth *et al*. showed that circulating IGF1 deficiency led to neurovascular dysregulation and a concomitant decline in cognitive function, akin to what is seen with aging (Toth *et al*. 2015). Therefore, these studies support the contention that circulating IGF1 has supportive and protective effects on cerebromicrovascular function.

Several therapeutic interventions involving GH/IGF1 have been investigated in ischemic stroke models. In hippocampal cell cultures deprived of oxygen and nutrients, IGF1 and IGFBP-ligand inhibitor prevented cell death (Mackay *et al*. 2003). Likewise, ICV administration of IGF1 resulted in reduced neuronal loss and improved neurological outcomes in several rodent models of hypoxic ischemic brain injury induced by arterial ligation (Guan *et al*. 1993, 2001, Schäbitz *et al*. 2001, Mackay *et al*. 2003) and IGF1 was more effective than insulin in protecting from neuronal loss (Guan *et al*. 1993). Similar results were reported in fetal sheep subjected to cerebral ischemia (Johnston *et al*. 1996). GH treatment via ICV administration improved motor function in endothelin-induced stroke in rats (Pathipati *et al*. 2009). Additional routes of IGF1 administration post neural ischemic injury, including intranasal (Liu *et al*. 2001, Fletcher *et al*. 2009, Lin *et al*. 2009), subcutaneous (Schäbitz *et al*. 2001), intramuscular (Chang *et al*. 2010) and intravenous (Rizk *et al*. 2007), have also been shown to be effective. Interestingly, administration of human marrow stromal cells improved functional recovery in rats with MCAO-induced ischemic infarcts and was associated with an increase in IGF1 mRNA expression and IGF1R immunoreactivity in cells at the ischemic boundary and subventricular zones (Zhang *et al*. 2004). Administration of IGF1 also ameliorated the negative effect of estrogen on ischemic stroke in middle-aged rats (Selvamani & Sohrabji 2010). ICV injection of adeno-associated viral vectors containing human IGF1 has been shown to promote prolonged functional recovery and enhanced neurogenesis after ischemic injury in mice (Zhu *et al*. 2008, Liu *et al*. 2017). In another study, antagonists targeted at IGF1 signaling-related miRNAs promoted neuroprotection (Selvamani *et al*. 2012). Although the evidence examining the links between IGF1 and cerebrovascular disease has been somewhat ambiguous in humans, when paired together with molecular and animal studies, the results indicate that IGF1 is likely a beneficial factor for cerebral vasculature and aids in neuronal recovery after an ischemic injury.

The 'strange case' of IGF1 in the aging brain: Dr Jekyll or Mr Hyde?

When taking into account the full breadth and depth of the evidence examining the role of IGF1 on brain aging and its related diseases, as summarized in Fig. 1, substantial uncertainty continues to surround many aspects related to this pleiotropic hormone in the CNS. While it is not yet entirely clear how to reconcile many

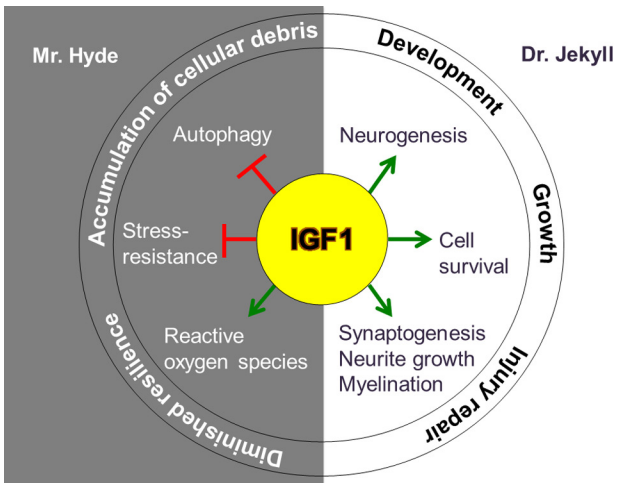

Figure 1
IGF1 playing the roles of Dr Jekyll and Mr Hyde in the brain. IGF1 exerts its beneficial effects on the brain by stimulating neurogenesis, synaptogenesis, neurite growth, myelination and promoting cell survival. These processes are important during early life for proper brain development and growth, whereas during aging, they contribute to repair of injured neural tissue, as may result from a stroke. On the other hand, the adverse effects of IGF1 on the brain include generation of reactive oxygen species and inhibition of both autophagy and stress responses. Inhibition of these functions results in diminished cell resilience and accumulation of cellular debris, which are characteristic of age-related neurodegenerative conditions such as AD and PD. AD, Alzheimer's disease; IGF1, insulin-like growth factor-1; PD, Parkinson's disease.

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of these conflicting findings reported across animal and human studies, a closer look at the subtle, but important, nuances and inconsistencies could begin to shed some light on the subject.

The effect of aging on the brain

Whereas it has been well-established that IGF1 is required for normal brain development (Woods *et al*. 1996, Kranzler *et al*. 1998, Abuzzahab *et al*. 2003, Netchine *et al*. 2011), its role in the aging brain has been less clear. Although most evidence from rodent models suggests that interventions that raise IGF1 level in the brain are beneficial to an otherwise healthy aging brain, studies in humans or disease models have not been consistently confirmatory. After early life development, the CNS shifts priorities from growth and expansion to preservation. Thus, maintaining the same robustness of IGF1 signaling throughout the lifespan, as during development, may actually be counterproductive or even harmful, as IGF1 signaling is known to attenuate pathways that promote cell preservation through stress resistance, reduction of oxidative stress and proteostasis (Barzilai *et al*. 2012). Since aging is the greatest risk factor for neurodegenerative disorders that are accompanied by abnormal protein deposition, such as AD and PD (Martinez-Vicente & Cuervo 2007, Kaushik & Cuervo 2015), the physiologic decline in IGF1 that accompanies aging may serve a protective role against these disorders by promoting an environment favoring clearance of dysfunctional proteins and cell maintenance. On the other hand, older adults may benefit from temporary elevations of IGF1 in settings of acute neuronal injury, such as a stroke or traumatic brain injury (Bianchi *et al*. 2017), where neuroregeneration regains priority over maintenance. This hypothesis is supported by findings that most models of AD benefit from reduced IGF1 signaling. On the contrary, in models of acute ischemic injury, higher IGF1 improves recovery (Bondanelli *et al*. 2006, Åberg *et al*. 2011). However, PD models need to be interpreted with caution. While IGF1 appears to be protective against DA neuron loss in models that induce SN injury, this approach is more reminiscent of acute neuronal injury that occurs with sudden ischemic or traumatic injury rather than the progressive, neuronal degeneration that is characteristic of PD in humans. Interestingly, decreased signaling via the IIS in invertebrates conferred protection from abnormal alpha-synuclein accumulation (Knight *et al*. 2014). Thus, the role of IGF1 in PD should be further investigated in more representative models of the disease.

Limitations of human observational studies

Endocrine pathways, including the somatotropic axis, are dynamic, adaptive and complex. Therefore, hormone secretion and bioavailability may vary widely in response to physiologic stressors in an effort to maintain desired homeostasis. This was highlighted by a study in which trajectories of IGF1 levels predicted mortality better than absolute levels (Sanders *et al*. 2017). Stress and illness can attenuate somatotropic signaling via changes in GH pulsatility and GH resistance (Van den Berghe 2001). Alternatively, a low IGF1 level may be a consequence of AD or PD and serve as a marker of more severe disease, as there is evidence that amyloid plaques and neurofibrillary tangles accumulate in the hypothalamus in patients with neurodegenerative diseases and disrupt endocrine function (Ishii & Iadecola 2015). Yet another theory, for which there is some supportive evidence, is that the reduction in IGF1 may be a compensatory mechanism employed by the body to shift resources away from proliferation and toward cell maintenance, in an effort to preserve neuronal function (George *et al*. 2017), and thereby limit the accumulation of cellular debris and damage during the aging process. On the other hand, a low IGF1 level may reflect lifelong low IGF1 due to presence of genetic variants. Similarly, an elevated IGF1 level may be inherited (Suh *et al*. 2008). Furthermore, peripheral levels may have no association with CNS signaling due to adaptive responses induced to protect vulnerable cells in the brain (Talbot *et al*. 2012, George *et al*. 2017). In contrast, IGF1 levels may rise in response to neuronal injury in an effort to repair damaged neural tissue. These biological scenarios demonstrate that the same measured IGF1 level may reflect different physiologic processes that may be distinguished only through long-term longitudinal follow-up and genetic studies.

IGF1 levels versus function

Most clinical observational studies focus on a single molecular phenotype, such as level of IGF1, as a surrogate of the somatotropic axis signaling (Al-Delaimy *et al*. 2009, Westwood *et al*. 2014, Doi *et al*. 2015, Ostrowski *et al*. 2016, Tumati *et al*. 2016). However, given the complexity of the pathway and its many interacting components, it is apparent that the function of the pathway cannot be reliably interpreted by merely measuring IGF1 levels. For example, such an approach could be misleading in individuals harboring functional *IGF1R* mutations that result in elevated IGF1 levels due to IGF1R resistance,

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thereby misclassifying them as having enhanced IGF1 signaling rather than reduced (Suh *et al*. 2008, Tazearslan *et al*. 2011). Similarly, IGF1 resistance at the level of the IGF1R and IRS-2 in the brain that accompanies certain disease states could potentially explain the compensatory elevations observed in serum IGF1(Talbot *et al*. 2012, Trueba-Saiz *et al*. 2013). More accurate characterization of IGF1 signaling in human studies can be achieved by accounting for the functional genetic variants in the genes that code for key intermediates of the somatotropic pathway and through functional studies.

Conclusion

Undeniably, genetic disruptions of endocrine GH/IGF1 signaling in experimental models have extended health span and lifespan. Although the models of brain aging are more complex, substantial advancements have been made in understanding the role of IGF1 in the aging brain. What ultimately determines the effect of IGF1 on the aging brain is the process that occurs in every dynamic biologic system: It is the ability of cells to modulate IGF1 signaling in an adaptation to the changing physiologic environment. Thus, the function of IGF1 in the CNS likely differs across the lifespan and different pathologic conditions. The results summarized above suggest that long-term maintenance of aging neurons, which are prone to the accumulation of cellular debris and damage that result in age-related neurodegenerative disorders such as AD and PD, benefits from reduced IGF1 signaling. On the other hand, recovery from an acute neuronal insult, such as a stroke, is augmented in the setting of higher IGF1. This evidence points to the fact that IGF1 indeed plays a double role in the aging brain, sometimes that of a good actor and at other times that of a bad actor, depending on the circumstance. Embracing this complexity may ultimately lead to better-targeted therapies for conditions that could benefit the aging brain.

However, before such strategies could be considered there still remain a number of important questions that need answers. These include (1) What is the relative contribution of autocrine vs endocrine-derived IGF1 in the aged CNS? (2) What is the effect of IGF1 on neurons vs on other cells found in the CNS, such as microglia, smooth muscle cells, endothelial cells and astrocytes? (3) What are the effects of acute vs chronic elevations of IGF1 in the aging brain? (4) Is low IGF1 a sign of accelerated aging or a genetically encoded protective mechanism in aging? (5) Is there an interaction between sex and IGF1 in the aging brain, as some studies suggest? (6) Are current experimental models of AD and PD good representations of human pathophysiology? (7) What is the effect of IGF1 signaling through the insulin receptor? (8) Are current genetic models of life-long disruptions of GH/IGF1 signaling representative of age-related IGF1 decline? (9) What are the differential effects of GH and IGF1? (10) Is low or high IGF1 a cause for, an adaptation to, or a consequence of disease? Some of these questions can be investigated in humans using longitudinal follow-up studies that thoroughly characterize participants phenotypically and genetically. However, many other questions will need to rely for answers on animal models. Therefore, the attempt to understand the relationship of IGF1 to brain aging and CNS diseases presents important challenges and opportunities to gain greater insight into how to invoke Dr Jekyll, rather than Mr Hyde qualities of IGF1 in the aging brain.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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