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Insulin-like Growth Factor 1 (IGF-1) as a marker of cognitive decline in normal ageing:

A review

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ABSTRACT

Insulin-like Growth Factor 1 (IGF-1) and its signaling pathway play a primary role in normal growth and ageing, however serum IGF-1 is known to reduce with advancing age. Recent findings suggest IGF-1 is essential for neurogenesis in the adult brain, and this reduction of IGF-1 with ageing may contribute to age-related cognitive decline. Experimental studies have shown manipulation of the GH/IGF-1 axis can slow rates of cognitive decline in animals, making IGF-1 a potential biomarker of cognition, and/or its signaling pathway a possible therapeutic target to prevent or slow age-related cognitive decline. A systematic literature review and qualitative narrative summary of current evidence for IGF-1 as a biomarker of cognitive decline in the ageing brain was undertaken. Results indicate IGF-1 concentrations do not confer additional diagnostic information for those with cognitive decline, and routine clinical measurement of IGF-1 is not currently justified. In cases of established cognitive impairment, it remains unclear whether increasing circulating or brain IGF-1 may reverse or slow down the rate of further decline. Advances in neuroimaging, genetics, neuroscience and the availability of large well characterized biobanks will facilitate research exploring the role of IGF-1 in both normal ageing and age-related cognitive decline.

1. Introduction

Mild Cognitive Impairment (MCI) is a term used to describe cognitive decline in the elderly that is more than that expected for normal ageing, but does not meet criteria for dementia. The diagnosis of MCI can be difficult, due to the heterogeneous nature of the syndrome, the

poor reliability of cognitive tests for detecting mild deficits, and the lack of available biomarkers which correlate with, or predict the development of MCI. MCI is itself is a risk factor for subsequent dementia, especially Alzheimer's disease, with a progression to dementia estimated at around 10–15% per year (Petersen et al. 2001). In 2016, the World Health Organization (WHO) reported that 47.5 million people have dementia, with an estimated 7.7 million new cases diagnosed each year. It was the 7th leading cause of death globally in 2015, with 1.54 million deaths (WHO 2017). Due to the increasing life expectancy in lower to middle income countries, the projected worldwide burden of dementia is expected to increase to over 150 million people by 2050 (WHO 2016). Research into the various causes of MCI and age-related cognitive decline is urgently needed, and the aim of this paper is to review one such possible cause, that the reduction in IGF-1 with ageing contributes to age-related cognitive decline.

There is consistent evidence that normal ageing is associated with declining activity of Growth Hormone (GH) and the GH/IGF-1 axis, resulting in reduced concentration of IGF-1 and reduced function of the IGF-1 signaling pathway (Brown-Borg et al. 1996; Milman et al. 2014; van der Spoel et al. 2015). This reduction is thought to contribute to the cognitive impairment that is seen in both human and animal models of ageing and dementia, and in humans, cross-sectional and longitudinal studies show the age-related decrease in IGF-1 is associated temporally with the subsequent development of cognitive impairment (Deak and Sonntag 2012; Licht et al. 2014; Sonntag et al. 2013; Sonntag, Brunso-Bechtold, and Riddle 2001). Both GH and IGF-1 deficiency syndromes are clinically associated with cognitive impairment in humans (Guevara-Aguirre et al. 2011; Deijen et al. 1996; van Dam et al. 2005; Trejo et al. 2007).

Circulating concentrations of IGF-1 can be increased by manipulation of the GH/IGF-1 axis via either daily injections of Growth Hormone Releasing Hormone (GHRH) (Vitiello et al. 2006; Baker et al. 2012) or peripheral administration of either GH or IGF-1 analogues (Trejo et al. 2007). Interventions designed to increase circulating IGF-1 via these mechanisms have been shown to improve learning and memory tasks and even reverse some effects of cognitive decline in some (but not all) studies (Ashpole et al. 2015; Deak and Sonntag 2012; Trejo et al. 2007; Baker et al. 2012; Vitiello et al. 2006; Sonntag, Brunso-Bechtold, and Riddle 2001; Arwert, Deijen, and Drent 2005; Oertel et al. 2004). Recently there has been interest in the evidence that physical activity and exercise can increase circulating IGF-1 concentrations in the elderly (Carro and Torres-Aleman 2006; Maass et al. 2016) and that exercise-induced stimulation of the GH/IGF-1 axis might improve cognition and hippocampal volume by stimulating hippocampal neurogenesis (Maass et al. 2016; Cassilhas et al. 2007; Carro and Torres-Aleman 2006).

The aim of this paper is to review the current evidence for the role of IGF-1 in cognitive decline in humans, and to review the current state of potential interventions based on the GH/IGF-1 signaling pathway as a means of either (1) predicting, or (2) preventing age-related cognitive decline. In order to fully appreciate the complexities and multiple actions of IGF-1, the remainder of the introduction will briefly review the current understanding of the physiological actions of IGF-1 and its effects on brain development, the adult brain, neurogenesis and longevity.

1.1 What is IGF-1?

IGF-1 is a single chain peptide (7.5 kDa) involved in many physiological, anabolic and metabolic processes throughout the body and is considered a major homeostatic regulator with a role in growth, development, life-span control and ageing. IGF-1 is approximately 99% protein bound in the circulation to one of six currently known binding proteins, of which insulin-like growth factor binding protein-3 (IGFBP-3) is the most abundant within the circulation (Holly and Perks 2012). Other binding proteins are more prominent in tissues, with IGFBP-2, -4 and -5 being more highly expressed in the brain, although the functional importance of these binding proteins is incompletely understood (Werner and LeRoith 2014; Bartke, Sun, and Longo 2013). After IGFBP degradation by proteases, IGF-1 can leave the circulation in the 'free' (biologically active) form or, in combination with one of the smaller IGFBPs (Janssen, Lely, and Lamberts 2003; Baxter 2000). Although IGF-1 can be produced in almost all bodily tissues in a paracrine/autocrine manner, the liver produces approximately 75% of circulating IGF-1 in humans, along with almost all of its binding proteins (Holly and Perks 2012; Yakar et al. 1999). Hepatic production of IGF-1 is regulated mostly by the actions of GH, however, insulin has also been shown to upregulate GH receptors and potentiate hepatic IGF-1 secretion (Leung et al. 2000).

Cellular actions of IGF-1 are mediated through activation of IGF-1 tyrosine-kinase membrane receptors. IGF-1 binds its receptor (IGF-1R) at the cell surface, initiating complex intracellular cascades and activating the phosphorylation of the insulin receptor substrate molecules, the phosphoinositide 3-kinase-protein kinase B (PI3K-Akt) pathway, and the mitogen-activated protein kinase (MAPK) signaling cascade (Holly and Perks 2012; Bondy and Cheng 2004). These activations have regulatory effects on two pathways known to be involved in cellular

ageing; the mechanistic target of rapamycin (mTOR) activity and the Forkhead box O (FoxO) translocation (Willcox et al. 2008; Bondy and Cheng 2004).

1.2 The GH/IGF-1 Axis

Hepatic production of IGF-1 occurs in response to Growth Hormone (GH) secretion from somatotrophs in the anterior pituitary. Growth Hormone Releasing Hormone (GHRH) from the hypothalamus, dietary proteins and ghrelin can all stimulate pituitary GH release, while IGF-1, somatostatin and insulin can all act to inhibit GH release (Popovic et al. 2003; Ceda et al. 1985). The GH/IGF-1 'axis' usually refers to the typical endocrine feedback mechanism between the hypothalamus, the pituitary and the resultant release or inhibition of GH and IGF-1, as shown in Figure 1.

GH is secreted in a pulsatile manner, the majority of which occurs nocturnally in association with slow-wave sleep, thus directly measuring GH levels as a routine biomarker can be problematic, with widely fluctuating levels over a 24-hr period (Sonntag, Ramsey, and Carter 2005; Ohlsson et al. 2009). Although the release of GH is pulsatile, its effect on IGF-1 remains relatively stable with minimal variability of IGF-1 concentration in a single individual (Borofsky et al. 2002; Deijen, Arwert, and Drent 2011). Despite these differences, the total serum concentrations of both GH and IGF-1 in humans reaches a peak around the second decade, then progressively declines until reaching a **relatively steady level** around the sixth decade (Yamamoto et al. 1991). Peak IGF-1 serum concentration around puberty in any individual are approx. 400 ng/mL and this reduces to around 100 ng/mL by the age of 75 years (van Dam and Aleman 2004).

Figure 1. The Growth Hormone/Insulin-Like Growth Factor-1 Axis.

INSERT FIGURE 1 HERE:

Key: GHRH – Growth Hormone releasing hormone; IGF-1 – Insulin-Like Growth Factor 1; IGFBPs – Insulin-Like Growth Factor Binding Proteins; BBB – Blood Brain Barrier; CSF – Cerebrospinal Fluid.

1.3 IGF-1 in Brain Development

IGF-1 plays a critical role in normal brain development. Mutations in IGF-1 and IGF-1 Receptor (IGF-1R) genes result in microcephaly and mental impairment (Abuzzahab et al. 2003; Juanes et al. 2015). Homozygous deletion of both IGF-1 and IGF-1R results in >90% lethality (Liu et al. 1993), and in IGF-1 and IGF-1R knockout mice there is reduced brain size, loss of myelination and behavioral deficits (Beck et al. 1995). Accordingly, transgenic mice with an overexpression of IGF-1 have a significantly larger brain size and an increase in myelin content and number of neurons (Carson et al. 1993; Sun et al. 2005). In humans, GH/IGF-1 deficiencies in childhood and adolescence result in reduced growth, short stature, reduced muscle mass and cognitive impairment, all of which can be reversed by administration of GH or IGF-1, depending on the nature of the primary deficiency (Laron and Kauli 2016; Ashpole et al. 2015). Interestingly, there are reports of normal cognition and intelligence in individuals with Laron dwarfism, an autosomal recessive condition characterized by various molecular defects in the GH receptor, resulting in very low circulating IGF-1 and IGFBP-3. Differences in the molecular defect responsible resulted in marked cognitive differences, with normal intelligence being seen in patients with the E180 splice mutation in exon 6, suggesting that

other unknown factors related to the molecular defect itself may be responsible (Shevah et al.

2005). In contrast to childhood or juvenile-onset GH/IGF-1 deficiency, cognition is rarely impaired in adult-onset GH/IGF-1 deficiency. Instead, clinical syndromes result in cardiovascular changes (Cuocolo et al. 1996), abnormal lipoprotein profiles (Cuneo et al. 1993) and impaired insulin tolerance rather than cognitive impairment per se (Johansson et al. 1995), thus highlighting the important role that IGF-1 plays in neurodevelopment.

1.4 IGF-1 in the Adult Brain

Circulating IGF-1 readily crosses the blood brain barrier (BBB) into the cerebrospinal fluid (CSF) and brain parenchyma via a saturable transport system, hence increasing peripheral circulating IGF-1 concentration results in a corresponding increase within the brain up to the point of transporter saturation (Piriz et al. 2011; Pan and Kastin 2000; Muller et al. 2012; Bondy et al. 1992). The choroid plexus is considered the primary route of entry into CSF (Carro and Torres-Aleman 2006).

Despite its ability to cross the BBB into CSF, local paracrine production is thought to be the major source of IGF-1 within the brain, (Torres-Aleman 2010; Sun et al. 2005; Bondy et al. 1992) and all types of cells within the brain are capable of IGF-1 production (Bartke, Sun, and Longo 2013). Initially, this local production was thought to be a homeostatic mechanism to maintain brain concentrations if circulating IGF-1 is low, however this is now thought to be influenced by a wider range of factors. A study by Muller et al (2012) showed local production of IGF-1 within the brain in mice was insufficient to compensate for the decrease in circulating IGF-1 that occurs with age, and they suggested age-related disruption of brain IGF-1 function might be causally related to cognitive decline (Muller et al. 2012). There is ongoing debate as

to whether locally produced paracrine IGF-1 plays a different role or has any functional differences to systemically produced IGF-1.

Mechanisms underlying **age-related** cognitive decline are not fully understood, although reductions in the number of synaptic connections between neurons is the most consistent correlate (VanGuilder et al. 2010; Sonntag et al. 2000). IGF-1 has effects via its signaling pathways on synaptic morphology and function, neuronal excitability and interactions with NMDA receptors, all of which are thought to have an important role in cognitive decline (Calvo et al. 2013; Shi et al. 2005; Sonntag et al. 2000). IGF-1 has been shown to enhance glutamatergic transmission in hippocampal neurons via a PI3K-mediated mechanism in old, but not young rats (Molina et al. 2013). The NMDA receptor is differentially regulated in ageing, and impairments in its expression and regulation have been proposed to lead to significant alterations in learning and memory (Magnusson, Brim, and Das 2010; Magnusson 2012). Indeed, supplementation of IGF-1 in aged rats has been shown to restore these age-related alterations in the expression of the NMDA receptor or its subunits (Sonntag et al. 1999; Sonntag, Brunso-Bechtold, and Riddle 2001; Le Greves, Le Greves, and Nyberg 2005; Le Greves et al. 2002).

Increased IGF-1R densities have been identified throughout the adult brain, however higher IGF-1R protein expression occurs in specific functional areas, including the hippocampus, amygdala, thalamus, hypothalamus, choroid plexus and parahippocampal gyrus (van Dam and Aleman 2004; Calvo et al. 2013; Deijen, Arwert, and Drent 2011; Sonntag et al. 2013). These brain regions are associated with mood, cognition and memory, supporting the idea that reduced IGF-1 (resulting in reduced function in these areas) may contribute to the memory impairments and cognitive decline often seen with ageing.

1.5 IGF-1 and Ageing/Longevity

The insulin/IGF-1 signaling pathway is believed to have a role in the control of ageing, and is evolutionarily conserved throughout species (Bartke, Sun, and Longo 2013; Bartke, List, and Kopchick 2016). Ageing is associated with a reduction of circulating IGF-1 as well as changes in brain IGF-1 receptor density (Deijen, Arwert, and Drent 2011; Sonntag, Ramsey, and Carter 2005). Reduced signaling of the GH/IGF-1 axis is associated with increased longevity in many studies, and in contrast, increasing circulating IGF-1 promotes the ageing process via oxidative stress mechanisms, and the promotion of cancer cell development and growth (Milman, Huffman, and Barzilai 2016; Piriz et al. 2011; Trejo et al. 2007). Humans with genetic variations in genes controlling elements of the GH/IGF-1 pathway that result in attenuation or partial resistance to IGF-1 have increased longevity (van der Spoel et al. 2015; Milman et al. 2014). Proposed mechanisms for increased longevity include enhanced insulin sensitivity and reduced insulin levels, reduced inflammation, reduced adipose tissue and increased Adiponectin levels (Bartke 2016). Although evidence suggests that declining function of the GH/IGF-1 axis may be beneficial for longevity, it is not clear at what stage of the lifespan this protection is conferred, nor are the mechanisms underpinning the apparent protective role against ageing fully understood (Bartke 2016). Several epidemiological studies of individuals with exceptional longevity found that genetic variations linked to IGF-1/GH signaling are over-represented in these cohorts (Van Heemst et al. 2005; Suh et al. 2008; Tazearslan et al. 2011; Gombard et al. 2012; Milman et al. 2014). These studies further support the role of the GH/IGF-1 axis in human longevity.

Reduced signaling may be associated with longevity, and conversely, there is robust evidence that increasing circulating IGF-1 promotes the ageing process via oxidative stress mechanisms and the promotion of cancer cell development and growth (Torres-Aleman 2010; Trejo et al. 2004; Piriz et al. 2011; Milman, Huffman, and Barzilai 2016). Many studies have linked higher IGF-1 concentration with an increased risk of cancers in human populations (Cao et al. 2015; Key et al. 2010; Rinaldi et al. 2010; Renehan et al. 2004). The mechanism is thought to be via activation of the IRS/Akt/MAPK pathway by IGF-1, which is known to promote cell growth and proliferation (Novosyadlyy and LeRoith 2012).

IGF-1 also appears to be an important regulator of vascular health, and age-related decline in IGF-1 is also thought to contribute to vascular mechanisms of ageing (Sonntag et al. 2013; Toth et al. 2015). A mouse model of IGF-1 deficiency showed cerebromicrovascular dysfunction and neurovascular uncoupling which mimicked the ageing phenotype, with subsequent deficits in hippocampal-dependent spatial memory testing (Toth et al. 2015). Neurovascular uncoupling has recently been implicated in both the development of cognitive impairment associated with ageing, as well as the development of Alzheimer's disease (Tarantini, Tran, et al. 2016).

However, research related to the role of IGF-1 in longevity and ageing remains inconsistent and is beyond the scope of this review. A recent detailed review of the GH/IGF-1 axis in human ageing is available (Milman, Huffman, and Barzilai 2016).

1.6 IGF-1 and Neurogenesis

IGF-1 is thought to play an essential role in brain neurogenesis, angiogenesis, beta-amyloid clearance, neuronal trophic support and other metabolic functions (Piriz et al. 2011; Torres-Aleman 2010; Bartke, Sun, and Longo 2013). Endogenous IGF-1 is now known to be the essential regulator for the differentiation of adult stem cells into neurons, with earlier in-vitro studies showing for the first time that neurogenesis in the adult is not only possible, but requires IGF-1 to do so (Brooker et al. 2000; Drago et al. 1991). Animal and in- vitro studies have demonstrated that increasing IGF-1 concentrations via administration of exogenous IGF-1 or manipulation of the GH/IGF-1 axis resulted in (a) increased neuronal acetylcholine release, (b) activation of NMDA receptors, (c) improved glucose utilisation, (d) cerebrovascular protection (Sonntag et al. 2013; Tarantini, Tucsek, et al. 2016) and (e) regulation of synaptic morphology and function (Ashpole et al. 2015; Nyberg and Hallberg 2013). Although IGF-1 is the principal ligand for mediating neurogenesis in both the developing and the adult brain, the intracellular pathways downstream of the IGF-1 receptor are ~~still being yet to be fully~~ characterized. A novel signaling pathway, the IGF-1-RIT1-Akt-Sox2 pathway, has recently been shown to play a critical role in IGF-1 dependent neurogenesis, pro-neuronal gene expression and increased cellular proliferation in hippocampal neuronal precursor cells (Mir et al. 2017).

It is now established that increased local IGF-1 paracrine production occurs as a result of brain injury (Torres-Aleman 2010) and furthermore, increasing brain IGF-1 concentrations after neuronal injury is associated with better recovery (Licht et al. 2014; Aberg et al. 2011; Markowska, Mooney, and Sonntag 1998). Administration of IGF-1 has recently been shown to improve recovery and cognitive outcomes following animal models of stroke and brain injury, as well as showing a benefit for the prevention of cognitive decline in older people (Carlson 2015; Lioutas et al. 2015; Sonntag et al. 2013). IGF-1 has both a rapid effect within minutes to

hours via changes in neuronal excitability (Nunez, Carro, and Torres-Aleman 2003), as well as delayed effects that are thought to be regulated through neurogenesis, angiogenesis or effects on glutamate synapses (Trejo et al. 2007), and it is thought that these short term changes are responsible for the improved recoveries seen in recovery from brain injuries when given IGF-1. However, given the very long-term changes in human cognitive decline, it remains unclear whether IGF-1 has any significant role in preventing cognitive decline in the elderly, or whether serum concentration simply reflects underlying neurodegeneration from ageing or other neurodegenerative disease processes.

2. Methods

A systematic review of the literature was undertaken in November 2016 using PubMed, Medline (EBSCO Host), CINAHL, PsychINFO and Embase. The search terms “(IGF-1 OR IGF1 OR insulin like growth factor OR growth hormone)” AND “(cognition OR cognitive OR dementia)” were used. A total of 6052 articles were then screened at title and abstract level, and 567 were selected for full text review. These were then further grouped into articles primarily concerned with IGF-1 and the following sub-categories: Ageing; Cognition; Alzheimer’s Disease; Delirium; Depression; Stroke/Brain Injury; Neurogenesis; and Other Neurodegenerative disorders. Many articles had overlap and were included in multiple groups as considered appropriate.

3. Results

Of the 567 articles selected for full text review, 193 were identified as primarily relating to IGF-1 and cognition, and assigned to the Cognition Group. These were further divided into animal studies (n = 57), human studies (n = 76), reviews (n = 36) and miscellaneous articles (n = 24). Of the 76 human studies identified in the Cognition Group, 25 involved healthy older adults, 13 used subjects with MCI or dementia, 11 studies used GH deficient patients and 27 studies involved various other disorders (Figure 2). A selective narrative review was undertaken, with a focus on IGF-1 and its relation to age-related cognitive decline of otherwise normal, healthy subjects, or those with early mild cognitive impairment. Specifically, articles relating to dementia, Alzheimer's disease, other neurodegenerative diseases, developmental or acquired GH or IGF-1 deficiencies were not included for the purposes of this review.

INSERT FIGURE 2 HERE (Search Strategy)

3.1 IGF-1 and Animal Studies

Many animal studies exist in the literature pertaining to the neurophysiology of the GH/IGF-1 axis and its effects on ageing, longevity and cognitive decline, however most used GH-deficient animal models, and showed that supplementation with GH or IGF-1 in these animals improved cognitive outcomes, particularly processing speed and spatial learning and memory (Sonntag, Ramsey, and Carter 2005; Toth et al. 2015; Le Greves et al. 2002). Although this gives valuable insight into the underlying physiology, it does not address the question of modifying the GH/IGF-1 axis in otherwise normal but aged animals to improve cognition, or

to prevent age-related cognitive decline. Interest has been sparked in this area due to the finding that increasing IGF-1 within the brain promotes neuronal recovery after injury, and thus administering IGF-1 may offer an alternative treatment modality promoting neurogenesis and recovery in patients after traumatic brain injuries or stroke (Aberg et al. 2011; Åberg et al. 2000; Toth et al. 2015; Lioutas et al. 2015).

Only a handful of studies used 'wild-type' aged animals instead of those with GH deficiency, thus giving insight into the potential for interventions to manipulate IGF-1 which may affect cognitive outcomes in normal ageing. One small study showed that intraventricular administration of IGF-1 to otherwise normal, aged rats ameliorated the decline in certain cognitive functions, and showed improvements in working memory and object recognition tasks (Markowska, Mooney, and Sonntag 1998). Daily subcutaneous GHRH injections in rats from 9 to 32 months of age prevented both the age-related decline in plasma IGF-1 levels and the cognitive decline seen in the aged-control group (Thornton, Ingram, and Sonntag 2000), suggesting the effect may have been mediated by IGF-1 and maintenance of the GH/IGF-1 axis as the animals aged. Although no underlying mechanism was suggested for this study, others have shown hippocampal neurogenesis occurs in normal aged rats following administration of either peripheral infusions of IGF-1 (Åberg et al. 2000), intra-cerebroventricular IGF-1 gene therapy (Pardo et al. 2016) and intraventricular IGF-1 (Lichtenwalner et al. 2001). Although hippocampal neurogenesis suggests a plausible mechanism for improved memory and cognitive outcomes following IGF-1 administration, it remains unclear if these immature neuron numbers directly correlate to improved cognitive functions or memory.

3.2 Human Observational Studies in Healthy Adults

Five independent small observational studies initially showed a correlation between serum IGF-1 concentrations and cognition in the late 1990's. (Morley et al. 1997; Paolisso et al. 1997; Rollero et al. 1998; Aleman et al. 1999; Arai et al. 2001). All of these studies were limited by small numbers and varying methodology, with differences in gender, age and health status of subjects, and differences in cognitive tests used for assessment, making comparisons and conclusions difficult. A more recent study also found a correlation between serum IGF-1 concentration and cognition in a group of 28 healthy, elderly subjects between 48-83 years of age (Bellar et al. 2011). Despite these findings, all of these studies had very small sample sizes, and positive results may have been subjected to publication bias, meaning that although promising, the results need to be interpreted cautiously. Table 1 summarises the human observational studies discussed in this section.

Table 1: Human Observational Studies of IGF-1 and Cognitive Outcomes

INSERT TABLE 1 HERE

Key: MMSE – Mini-Mental State Examination; RAVLT – Rey Auditory Verbal Learning Test; RVDLT – Rey Visual Design Learning Test; WAIS-III - Wechsler Adult Intelligence Scale 3rd edition; CANTAB – Cambridge Neuropsychological Test Automated Battery.

Kalmijn et al (2000) looked at a larger prospective sample, taken from the population-based Rotterdam Study, of 186 healthy participants aged between 55 – 80 years. After adjustment for age and other factors, serum total IGF-1 was inversely related to cognitive decline over the next 2 years (Kalmijn et al. 2000), in apparent contrast to earlier studies where lower IGF-1 was associated with poorer cognitive outcomes. Also of interest, they found no relationship

between free IGF-1 and cognition, which is thought to be more representative of the biologically active component of the total IGF-1 concentration. Free IGF-1 is also thought to be a better indicator of GH secretion than total IGF-1 (Janssen and Lamberts 1999; Janssen, Lely, and Lamberts 2003), and the Kalmijn study concluded that factors other than GH secretion are involved in the relationship of total IGF-1 to cognitive decline. This is an interesting hypothesis as it means potential interventions which increase GH may not have the desired effect of improving cognitive outcomes, and it may be something to do with IGF-1 itself, or even an independent action of the various binding proteins.

However in apparent contradiction to this, Quik et al (2012) did find a significant correlation between peak concentrations of GH secretion and cognitive performance in 17 elderly male patients when given selective attention tasks (Quik, Conemans, et al. 2012). IGF-1 serum concentrations and cognitive tasks were measured on a single day, after stimulation of GH release by administration of GH-RH. A similar pattern was seen in patients with GH deficiency following cranial irradiation for the treatment of non-endocrine brain tumors, where those with reduced GH secretion after GH-RH stimulation showed poorer results in cognitive and memory tasks performed on the same day (Quik, Valk, et al. 2012). These two studies have methodological limitations given the confounding due to underlying illness, and both were looking at rapid short-term effects of GH on cognitive tasks performed within hours of GH release, and not on longer term GH control of IGF-1 and its relationship to cognitive decline in ageing.

Dik et al (2003) published a much larger prospective study (n=1318) following a cohort of subjects aged 65-88 years over a 3-year period, and found total IGF-1 directly related to various cognitive parameters, including MMSE scores on cross-sectional analysis. Although

the associations were not significant after adjustment for age, they did identify a 'threshold effect' whereby those in the lowest quintile of IGF-1 showed slower information processing speed at baseline and at 3-year follow up (Dik et al. 2003). No gender differences were identified and they concluded that low concentrations of IGF-1 ($<9.4\text{nmol/L}$) were associated with both lower cognitive scores and a greater decline in cognition, specifically on information processing speed (Dik et al. 2003).

A longitudinal study by Okereke et al (2006) looked at the relationship between midlife plasma free IGF-1 and subsequent late-life cognitive function in 376 older men. Using stored samples from approximately 18 years earlier for baseline free IGF-1 levels, it was shown that midlife concentration of free IGF-1 was positively correlated to cognitive performance in later life. Results indicated that after adjustment for age and various health and lifestyle factors that each standard deviation (SD) increment in free IGF-1 was associated with a multivariable-adjusted increase of 0.08 units on global scores of cognitive performance (Okereke et al. 2006). This difference in cognitive scores was equivalent to that observed between men 2 years apart in age, indicating that each SD higher level of free IGF-1 appeared to be the cognitive equivalent of men aged 2 years younger, and they concluded that a higher midlife concentration of free IGF-1 might be associated with better late-life cognition (Okereke et al. 2006).

Interestingly, a follow up study by the same author in 2007 using a female cohort of 590 subjects showed a similar trend, but the differences were less pronounced, with each SD of IGF-1 the cognitive equivalent to 1 year of age difference (Okereke et al. 2007). It was noted that the age range of this cohort was much narrower compared with the male only study, which may explain the difference, but it may also reflect gender differences in IGF-1 and/or

the GH/IGF-1 axis. This gender difference was also identified in a study by Al-Delaimy et al (2009) whereby IGF-1 levels were positively correlated with MMSE and verbal fluency in elderly, otherwise healthy men (n=636) but not women (n=899) (Al-Delaimy, von Muhlen, and Barrett-Connor 2009). No mechanism for this gender difference was identified.

A single baseline measure of IGF-1 could be related to better memory performance in subsequent years. A small study (n=30) with healthy adults between 41 – 76 years of age showed that subjects with higher IGF-1 had better memory test performance 4 years later (Deijen, Arwert, and Drent 2011). A more recent and larger (n=400) prospective study showed a similar result with a longer 8-year follow up in middle aged and older men (Tumati et al. 2016). Results from both studies indicate that a higher midlife free IGF-1 concentration may be associated with better late-life cognition. Interestingly, in the Tumati study, both high and low serum concentrations of IGF-1 were associated with poorer cognitive function, suggesting a “U-shaped” curve where optimal levels of IGF-1 for cognition maybe somewhere in the middle range. However, serum IGF-1 concentrations were not recorded at follow-up, thus the poorer cognitive outcomes may have been associated with individual changes in IGF-1 over time, rather than baseline levels.

Of note is a finding using data from the English Longitudinal Study of Ageing, where the association between serum IGF-1 and symptoms of depression in older people also showed a “U-shaped” pattern, with lowest risk seen around median concentrations of IGF-1 (Chigogora, Zaninotto, and Batty 2015). Although this study did not measure cognitive parameters per se, Lin et al (2014) did show a correlation between low IGF-1, depressive symptoms and cognitive impairment in a small cross-sectional study of 94 healthy older adults (Lin et al. 2014). While neither of these studies could identify if the relationship was causal, both

concluded interventions that result in increasing IGF-1 might be a novel approach to slowing cognitive decline in older persons, especially those with depressive symptoms (Chigogora, Zaninotto, and Batty 2015; Lin et al. 2014). However, the association between depression and cognitive decline remains unclear, and the potential harm from such an intervention is also unknown, so it would be difficult to advocate such an approach without further elucidation of the underlying mechanisms.

Data was analysed from a retrospective survival cohort of 901 older adults over 65 years of age from the CHS All Stars study comparing changes in circulating biomarkers with functional decline over a 9-year period (Sanders et al. 2014). Although they concluded that various biomarker changes were poorly correlated with functional decline overall, they did find that IGF-1 was correlated to decline in cognitive function ($p=0.04$) when viewed separately from physical functional decline measures (Sanders et al. 2014). They did not look at gender differences within the group.

In contrast, a study using data from the Amsterdam Growth and Health Longitudinal Study, found no association between IGF-1 and cognition, although the mean age of the 277 participants was 42.4 years (Licht et al. 2014). This is a much younger cohort than previous studies where associations between IGF-1 and cognition were found, and it would be interesting to review cognitive testing on this cohort in 10 – 20 years, to see if an association becomes apparent in later life. IGF-1 as a biomarker of cognitive performance is less valuable in a younger adult population, and as such, it is unlikely to show any correlation with cognitive performance in this group. Indeed, in most studies where positive correlations were identified the median age was over 60 years.

There is one recent cross-sectional study in older adults that is inconsistent with previous studies. In this study of very old Ashkenazi Jews over 95 years of age, women (n=163) within the higher tertile ranges of IGF-1 had worse cognitive results on MMSE testing (Perice et al. 2016). In this age group, they also found no association between IGF-1 concentrations and cognitive impairment in men, although the study only included a modest number of men (n=40) compared with 163 women (Perice et al. 2016). This is the first study to show no association between IGF-1 and cognition in older adults. Reasons for this remain unclear, but possible explanations include; (a) differences in study design, including self-reported measures that may result in recall bias (b) differences in the role of IGF-1 for cognition and neuroprotection at different decades in life, with this cohort being much older than other studies, and (c) possible genetic variance due to the homogeneity of the group.

Two recent studies have looked at IGF-1 concentrations in elderly people with known mild cognitive impairment (MCI). In a small study, IGF-1 concentrations in a clinical cohort of 31 elderly persons with MCI, higher serum IGF-1 was associated with better global cognition and better performance on tests of learning and memory (Calvo et al. 2013). In a larger population study of 3355 elderly participants, lower serum IGF-1 concentration was associated with poorer cognition in multiple domains, and was associated with MCI after adjusting for covariates (Doi et al. 2015). These results were taken from a single cross-sectional analysis, and do not give any indication on whether the ongoing rate of cognitive decline has any association with IGF-1. If this holds true, then interventions that increase serum or brain IGF-1 may be able to slow down or even prevent further cognitive decline in those with MCI.

3.3 Summary and Limitations of Human Observational Studies

In summary, these multiple studies show mixed evidence with regards to serum IGF-1 concentration and the long-term effects on cognition in the elderly. However, on balance the studies suggest a link may be present, but no causal relationship is identifiable in any study and methodological problems restrict direct comparisons. The most common correlation is a lower IGF-1 is associated with lower cognition, however the more recent studies have also shown a possible inverse correlation with high IGF-1 concentrations, suggesting that a possible “U shape” of IGF-1 concentrations which may result in poorer cognitive outcomes at both higher and lower ends of the range. Verifying this pattern provides a testable hypothesis and larger epidemiological studies would give further information and clarify whether the relationship is linear or indeed “U-shaped”. Of those already with MCI, there appears to be a stronger association between IGF-1 and cognitive performance, although the smaller studies are clinical cohorts and are subject to sampling bias. Due to the heterogeneity of MCI and the variation in disease course, much larger population studies are required, with standardized protocols to define MCI.

In all of these studies, it is important to also note that CSF or brain concentrations of IGF-1 were not measured. Given that paracrine production of IGF-1 in the brain itself has been postulated to be essential for neuroprotection and neurogenesis (Yakar et al. 1999) , serum IGF-1 may not adequately reflect the concentration of IGF-1 within the brain parenchyma. There is also methodological variation between studies with measuring IGF-1 itself, with some measuring total concentration (bound and free), and others just the free fraction. This may be an important differentiation as the biologically active form may not be the component being measured. Differences in binding and function of the six IGFBP's are still unclear, so differences in correlation with cognition may simply reflect differences in IGF-1 measurement techniques. Measuring the molar ratio of IGF-1/IGFBP3 has been suggested as an indirect

measure of the bioactive IGF-1 component (Juul et al. 1994), however it remains unclear as to whether total IGF-1, free IGF-1, the ratio of IGF-1/IGFBP3 or even measurement of any other IGFBPs gives the most accurate representation of the correlation between IGF-1 and cognitive outcomes. Furthermore, circulating IGF-1 concentrations do not necessarily reflect the activity of downstream intracellular signaling pathways. Thus, the overall concentration of circulating IGF-1 may have little correlation with its bioactivity per se, and may be influenced by alternative elements such as the IGF-1 receptor, or other molecules within the signaling pathway.

Kommenterede [JM1]: Yeah...this is a good point...we should keep this comments in mind when we move into UKB data..."limitations of the study" etc....

Another major consideration is the lack of consistency in type of cognitive testing undertaken between the studies, and the lack of any definition of what constitutes cognitive impairment. Different tests of overall or global cognition (such as the MMSE) can be very crude and although used as screening tests, are not diagnostic in their own right for cognitive impairment. More robust neuropsychological testing is required, especially to clarify specific areas of cognitive impairment, such as verbal processing or memory. As IGF-1 receptor densities differ between areas of the brain, performance on cognitive tasks that require hippocampal input may be more influenced by IGF-1 concentrations (Licht et al. 2014). The lack of consistency across the studies makes it difficult to determine or compare effects, and often, a person's underlying IQ is not known or taken into consideration in the analysis. Despite this, a meta-analysis in 2005 supported the positive association between IGF-1 and overall cognition in the elderly (Arwert, Deijen, and Drent 2005).

Finally, most studies have been retrospective cross-sectional studies which are often prone to reverse causation effects, or smaller clinical samples which are prone to selection bias. Much

larger, prospective longitudinal studies are needed in order to remove potential confounders and to establish not just correlation, but determine any direction of causation if one exists.

3.4 Human Clinical Intervention Studies

Clinical studies as far back as 1980 have shown significantly improved cognition and mental health in both children and adult patients with GH deficiency after treatment with GH substitution (Falleti et al. 2006; Deijen, de Boer, and van der Veen 1998; Deijen et al. 1996; Arwert et al. 2006). The suggestion that interventions relating to IGF-1 pathways could delay or reverse cognitive changes seen in ageing is a tantalizing prospect, however, only a few intervention studies exist in the literature regarding the effect on an otherwise healthy ageing population, as a method of cognitive ‘enhancement’ or, as a potential therapy to prevent cognitive decline. A summary of these is given in Table 2.

Table 2: Human Clinical Interventional Studies – modification of GH/IGF-1 axis and cognitive outcomes.

INSERT TABLE 2 HERE

Key: MMSE – Mini Mental State Examination; WAIS-R – Wechsler Adult Intelligence Scale Revised; HVL – Hopkins Verbal Learning Test

Papadakis et al (1996) used GH treatment for six months to increase IGF-1 concentrations of 52 healthy older men, but found no improvement in cognitive function at endpoint (Papadakis et al. 1996). Although the numbers in these studies are modest, the findings suggest that simply administering GH in order to increase circulating IGF-1 concentration in otherwise healthy older people may not lead to improved cognition or delay in cognitive decline, as was also suggested in the Kalmijn *et al* (2000) observational study discussed earlier in 3.2. This further supports the idea that a factor *other* than GH is involved in the cognitive outcomes seen with increased IGF-1. Furthermore, using GH in this way may in fact be harmful due to the increased risk of cancer, diabetes and cardiovascular disease that is known to be associated with GH administration.

A later study by Friedlander et al (2001) also reported no changes on either cognitive or psychological outcomes after one-year of low dose (15 µg/kg twice daily) injections of recombinant human (rh) IGF-1 compared to controls in healthy post-menopausal women over 60 years, however the study was discontinued after a futility analysis at the 1-year mark when interim results were available. Blood tests confirmed that circulating IGF-1 in the treatment group was elevated to the approximate level of that seen in young adults, but no cognitive differences were evident between either group (Friedlander et al. 2001). The same research group had previously shown a short-term benefit in these parameters with low dose (rh)IGF-1, but concluded that the effect on body composition and the so-called 'psychological aspects of ageing' was transient, and that long term therapy was ineffective (Friedlander et al. 2001). However, the very small numbers in this early pilot study (11 subjects and 5 controls) make conclusions difficult to generalize.

Instead of using (rh)IGF-1 directly as the treatment, a prospective, randomized, placebo-controlled, double-blinded trial by Vitiello et al (2006) examined the effect of six-months treatment with daily GHRH injections on subsequent cognitive outcomes in 89 healthy older adults between 60 and 85 years of age. They found circulating IGF-1 concentrations increased by 33.8% and cognitive functions improved by approximately 6% in the treatment group compared to those in the placebo group (Vitiello et al. 2006). They did not find the effect varied by gender or estrogen status. The study concluded that treatment with GHRH (used to increase endogenous IGF-1) could improve cognition in otherwise healthy men and women, although the mechanism was not understood.

Baker et al (2012) undertook a larger follow up double-blinded RCT, with 152 adults between 55 and 87 years of age (of which 66 had a diagnosis of mild cognitive impairment). Participants self-administered 1 mg injections of tesamorelin, a human GHRH analogue for 20 weeks (Baker et al. 2012). Circulating IGF-1 concentrations increased by 117% in the treatment group but remained within the physiological range equivalent to a young adult level, and favorable effects on cognition were seen in both the healthy and MCI subjects when compared to the placebo group (Baker et al. 2012). It is unknown whether the positive effect they reported was sustained longer term or not.

Overall, these four studies are disappointing with respect to improving or slowing cognitive decline in otherwise healthy, aged people. Despite the correlations seen between IGF-1 and cognition in the cross-sectional observational studies, and the positive outcomes seen with animal-model studies, these human interventional studies have not shown any clear benefit with GH or (rh)IGF-1 administration, and only a modest improvement in cognition with GHRH administration. All studies did show that an increase in peripheral IGF-1 concentration was

attained, however the mixed results on cognition again suggest another factor may be involved. It is important to note that administration of GH or GHRH as a method of increasing IGF-1 is likely to result in other unintended consequences as both of these hormones have their own metabolic functions independent from IGF-1. However, the study using (rh)IGF-1 did not show any improved cognitive outcomes, which further supports the idea that age-related cognitive decline may not be directly attributable to IGF-1, but an alternative factor or an independent action of GH/GHRH in the tissues via another mechanism. Again, no direct measures of brain IGF-1 concentrations were taken, and although peripheral IGF-1 concentrations were raised, it is not clear if this translated to increased brain concentrations. One further problem may be the short length of intervention time of these studies. Given that in humans, cognitive decline is a slow process which can take many years, it is likely that the short interventional time may not have been able to show any true improvement even if there was an underlying beneficial process occurring.

4.0 IGF-1 and Alzheimer's Disease

IGF-1 is involved in regulation of brain beta amyloid protein levels, which may contribute to age-related cognitive decline as outlined earlier, but may also play a role in the development of Alzheimer's disease (AD) and/or other dementias (Sonntag, Ramsey, and Carter 2005). Unsurprisingly, studies are now investigating the role of IGF-1 and its major binding protein **IGFBP-3** in the development of AD, not just its role in cognitive impairment and ageing (Almeida et al. 2017). IGF-1 appears to inhibit abnormal tau phosphorylation and beta-amyloid deposition in cell cultures and transgenic mouse models of AD (Westwood et al. 2014). There is also evidence that concentrations of IGF-1 are negatively correlated with brain

amyloid beta deposition in rats, suggesting that increasing serum IGF-1 could reduce the amyloid burden (Kimoto et al. 2016). Serum IGF-1 concentration also decreases as cognitive function becomes more impaired in AD (Kimoto et al. 2016). However, although evidence suggests it is again becoming clearer that although IGF-1 is may be involved in the physiological mechanisms of both neurogenesis and neurodegeneration, other mechanism related to IGF-1 receptor function or individual molecular components within the various IGF-1 mediated intracellular signaling pathways may yet prove to underpin contribute to the pathophysiological changes seen in Alzheimer's or other neurodegenerative diseases.

Kommenterede [JM2]: Hmm...long and complex sentence...may need to use more full stops ☺

It is beyond the scope of this paper to review all of the information with respect to IGF-1 and Alzheimer's disease specifically, however two recent studies are worth mentioning. In the large Framingham study cohort, lower IGF-1 concentrations were associated with greater risk of developing AD dementia, while higher concentrations were associated with greater brain volumes on Magnetic Resonance Imaging (MRI) (Westwood et al. 2014). In another recent study of patients with Alzheimer's disease, MMSE decline over time was steeper among participants with lower IGF-1, and for each decrease of 1 SD of IGF-1, subjects lost an additional 0.63 points per year in MMSE (Vidal et al. 2016). The conclusion drawn was that lower baseline serum IGF-1 was associated with faster cognitive decline in AD over a 2-year period (Vidal et al. 2016). However two different meta-analyses (Hu, Yang, and Gong 2016; Ostrowski et al. 2016) of IGF-1 in Alzheimer's disease were published in 2016, with varying conclusions, showing that evidence is still mixed and uncertain. The first meta-analysis did not find a significant association between IGF-1 and risk of Alzheimer's disease in either direction, although they did not take cognitive scores or stratification of disease progression into account (Ostrowski et al. 2016). The meta-analysis by Hu et al (2016) however did **stratify** the groups according to disease progression and by doing this, they found that

circulating IGF-1 levels were lower in AD patients than controls when studies of age difference >1 or 2 years were excluded, and that circulating concentrations of IGF-1 were associated with age as well as decreasing degree of MMSE scores (Hu, Yang, and Gong 2016). It is clear that the association between circulating IGF-1 and Alzheimer's disease is complex, multifactorial, and requires further investigation.

5.0 Genetics and IGF-1

Multiple early studies have shown an association between polymorphisms in the IGF-1 gene and serum IGF-1 concentrations, and it is estimated that up to 60% of the variance in serum IGF-1 concentration is thought to have a genetic basis (Licht et al. 2014; Hong et al. 1996). It has also been found to have a high heritability of ~40-60% (Hong et al. 1996; Kaplan et al. 2011). Several polymorphisms have been found in the promoter region of the IGF-1 gene, which are thought to contribute to the transcription rate of IGF-1 (Licht et al. 2014; Kato et al. 2003). The primary polymorphism is a variable length cytosine-adenosine (C-A) repeat, however the homozygote 192bp genotype has also been associated with both higher and lower IGF-1 concentrations when compared to the heterozygote or to non-carrier genotypes (Kato et al. 2003; Licht et al. 2014; Van Turenhout et al. 2011). Studies have also been attempting to identify the genes for the IGF-1 receptor, other downstream signaling molecules, and IGFBP3, given that it is the primary carrier protein for IGF-1 in the circulation and can affect bioavailability (Kaplan et al. 2011).

Licht et al (2014) attempted to look at the association between genotype, IGF-1 and cognition in younger adults, and although confirming an association between genotype and IGF-1 concentrations (the presence of the 192bp allele resulted in lower IGF-1), they did not find a

direct association with cognition. As was discussed earlier, this would be expected in a younger cohort, and follow up cognitive tests in 10-30 years' time would be necessary to establish any link.

In recent years there have been major developments based on Single Nucleotide Polymorphism (SNP)-derived, genome-wide metrics that capture disease risk estimates in the absence of knowing the precise nature of the individual risk alleles (e.g. number or location). For example, polygene risk scores can be derived from genome-wide association studies (GWAS). Briefly, based on case-control studies (for disease outcomes) or general population samples (for quantitative traits), odds ratios for particular variations at each SNP are estimated in a "discovery" sample (Evans, Visscher, and Wray 2009). Thus far, GWAS studies based on 30,884 individuals have identified seven genome-wide significant SNPs associated with IGF-1 concentrations (Kaplan et al. 2011; Teumer et al. 2016). However, much larger samples will soon be available, for example the UK Biobank that will have 500,000 samples (Sudlow et al. 2015). Once these estimates are available, polygene scores for IGF-1 concentrations can be compared with scores of a range of cognitive phenotypes, such as educational achievement, cognitive decline, or development and progression of dementia. Methods are now available that allow for summary score comparisons rather than individual genotypes (Bulik-Sullivan, Finucane, et al. 2015; Bulik-Sullivan, Loh, et al. 2015). Of particular interest for observational epidemiology, variants that contribute to SNP-based instruments are (a) inherited (and thus pre-date the onset of the disease outcome of interest), and (b) risk alleles are randomly divided during meiotic recombination (Mendelian Randomization) (Evans and Davey Smith 2015). These methods are expanding our ability to explore causal relationships, and may be well suited to exposures that have long latencies, as is often the case in age-related disorders. For example, a single cross-sectional assessment of IGF-1

concentration may not be indicative of cumulative exposure over many decades. However, the use of genetic instruments (polygene risk scores that predict IGF-1 concentration) may provide an efficient measure to identify individuals with variants associated with high or low IGF-1 concentrations. If small changes in IGF-1 concentrations are linked to cognitive outcomes, the methods can help support or reject hypotheses.

6.0 Discussion and Clinical Significance

It would appear that a reduction in IGF-1 and GH/IGF-1 signaling may prolong life and protect against cancer at the **expense** of cognition, which is somewhat of a paradox in that a mechanism to potentially improve lifespan results in reduced brain/cognitive function. It has been argued by some that this is an example of ‘antagonistic pleiotropy’ (Milman, Huffman, and Barzilai 2016; Bartke, List, and Kopchick 2016) whereby IGF-1 is important for early brain development and growth, but persistently high circulating IGF-1 in later life may pose a greater risk of malignancy and death. It is unknown at what time and/or duration of exposure to altered GH/IGF-1 concentrations are required for the ‘switch’ from beneficial effects to deleterious effect of higher circulating IGF-1. This second paradox of dosage also poses questions with regard to the timing of any intervention, the most recent data pointing towards a “U-shaped curve” of optimal IGF-1 circulating concentrations. Whereas higher serum IGF-1 in middle age does appear to be associated with a reduction in cognitive decline in later years, the data from the oldest of the old (>85 years) seems to show the opposite effect. This raises questions not just about dose, but also timing and duration of any potential intervention for cognitive outcomes. Given that human interventional studies have not shown the same benefit as animal studies in this area, there is obviously much more that needs to be understood.

Currently, the evidence linking IGF-1 and cognitive decline, either in ageing or with specific neurodegenerative diseases is mixed. Most of the studies are cross-sectional, observational or retrospective, and in the absence of randomized clinical trials, we cannot deduce causation based on these studies. It is feasible that IGF-1 by itself is not a useful screening tool at the present time, although it does appear a person's life-long concentration (or midlife level) may ultimately provide information as to an individual's future risk of cognitive decline. IGF-1 may well prove to be a useful biomarker to predict risk, and hence instigate preventative and early intervention strategies in middle age in order to prevent age-related cognitive decline. Further questions need to be answered before using serum concentrations, or better still, genetic markers to predict life-long exposure, in a screening role. It is still unclear at what age this would need to be done, and what interventions can actually work. Certainly, reduction of cardiovascular and other metabolic risk factors such as obesity and diabetes are useful, however it would be prudent to advise on improvement in these factors for the health of any person, regardless of IGF-1 status. Concentrations of IGF-1 do not confer any additional diagnostic information for those with suspected cognitive decline, and so the routine measurement of IGF-1 in a clinical sense is not currently justified. Even in cases of established cognitive impairment, it remains unclear whether increasing circulating or brain IGF-1 at that stage may reverse or even slow down the rate of further decline. It may give some prognostic information, however what this means for any individual case is not established.

The usefulness of IGF-1 as a therapy remains even more uncertain. Animal studies consistently show cognitive improvement after supplementation with IGF-1 (or increasing IGF-1 through modulation of the GH/IGF-1 axis), but corresponding human studies have been disappointing. There certainly appears to be a potential role for increasing IGF-1 concentration acutely in the brain following brain injury to promote neurogenesis, but its role

in chronic neurodegenerative disorders remains uncertain. In acute therapy, administration of IGF-1 via an intranasal route may provide a mechanism for administration directly to the central nervous system whilst minimizing any detrimental systemic effects, and may be a novel therapy for stroke or brain injuries in the future (Hanson and Frey 2008). However, as the long-term effects of such a treatment are unknown, especially the local effects of IGF-1 on respiratory mucosa, it would be foolish to recommend an intervention of this sort without any further long-term studies. This difference between short-term and long-term effects of IGF-1 on the brain is still unclear and needs further investigation. The potential risks associated with long term administration of IGF-1, GH or GHRH are likely to outweigh the potential benefits, given that increased IGF-1 is associated with increased risk of cancer and would promote the ageing process, potentially have the effect of shortening life-span. Thus, timing and dosage for the chronic administration of GH/IGF-1 axis 'modulators' in older adults to maintain hippocampal and brain function would be critical, and currently there is no clear answer to these questions based on the current literature.

An exception to this is may be increasing physical activity and exercise in the elderly is a promising intervention that modulates the GH/IGF-1 axis in order to increase IGF-1 towards younger concentrations. This has consistently been shown to improve cognition in animal studies, although human study results again have been mixed (Monteiro-Junior et al. 2015; Maass et al. 2016). This may turn out to be the simplest way to improve an individual's IGF-1 profile over time, with concentrations of IGF-1 staying within the individual's physiological range, to help ameliorate the cognitive decline that can occur with ageing. Studies are currently under way in elderly populations specifically addressing this issue, and trying to quantify the level and type of physical exercise that is required to maintain optimal brain health.

6.1 Directions for Future Research

Further research is needed as highlighted in the previous section with regards to clinical applications for diagnostic, prognostic and therapeutic information. Larger, longitudinal prospective studies are needed in order to elucidate underlying mechanisms and answer some of these questions. Specific questions arise for each different population subgroup – those who are ageing but otherwise healthy; those with cognitive impairment; those with Alzheimer’s and/or other neurodegenerative conditions, and those with acute brain injuries. Studies are also needed to determine if the rate of cognitive decline is related to IGF-1 concentration once cognitive impairment is established, and the potential reversibility of age-related cognitive decline.

The effects of gender on the role that IGF-1 plays in ageing, cognition and its role as a neuroprotective agent needs further clarification. To date, gender differences are becoming more apparent in a number of studies, although no explanation for the mechanism has been established. Of note, many of the original animal studies were performed using male animals, and it may come to pass that this is why animal studies have had more promising results than human ones. In human studies the effects of IGF-1 on cognition have not been as evident in females, and this sex-related difference needs further investigation.

Finally, genetics will play an important role to guide research in this area. Given the strong genetic link with IGF-1 concentrations and the heritability of the gene, and with preserved GH/IGF-1 pathways genetically conserved across species, it follows that variations in genetic markers may provide clues as to underlying mechanisms and correlations between IGF-1 and

cognition. Use of modern GWAS techniques and the availability of large research biobanks will allow for much larger genetic and epidemiological studies to clarify the relationship further

7.0 Conclusion

Despite extensive research over the past 30 years into the biology of IGF-1 and the GH/IGF-1 axis and signaling pathways, the precise relationship between IGF-1 and cognition remains unclear. Animal studies have shown promise, however human clinical trials have remained overwhelmingly disappointing in both elucidating underlying mechanisms and in identifying or preventing cognitive decline. Mendelian randomization studies will provide information on common genetic variants that code for IGF-1, and if these are shown to predict cognitive and brain outcomes, further interest in IGF-1 and cognition will be generated.

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Five Key Points

1. IGF-1 has a major role in growth, ageing, brain development and adult brain function.
2. Animal studies support the link between IGF-1 and cognition and other brain outcomes.
3. Links between IGF-1 and normal cognition in human studies are mixed.
4. IGF-1 reduces with age and precedes cognitive decline in the elderly, however a clear causal relationship has not been identified.
5. Mendelian randomization and genome-wide association studies of IGF-1 may be able to provide clues with respect to causality and cognition.

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