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IGF-I and the aging mammalian brain

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ABSTRACT

Insulin-like growth factors (IGFs) are important modulators of organismal life-span all along phylogeny. These growth factors are widely viewed as detrimental for long life by reducing tissue resistance to oxidative stress. However, IGF-I has been consistently shown to be a potent neuroprotective factor in mammals, and as such, a deterrent of brain aging. Conversely, recent data suggest that IGF-I may contribute to amyloid neurodegeneration underlying Alzheimer's disease. These opposing observations underline an incomplete understanding of the significance of this ancestral hormone pathway in relation to brain aging. It is possible that these opposite results are the consequence of using different experimental approaches. Thus, brain amyloid injury is reduced in mutant mice partially defective in IGF-I receptor function, whereas IGF-I is neuroprotective when administered to animal models of neurodegenerative disease or normal brain aging. This approach-dependent effect of IGF-I highlights a fundamental gap in our knowledge of the relationship between peripheral and brain IGF-I function and the actual biological impact of experimental modulation of brain IGF-I function. We suggest to directly address brain IGF-I function in the varying experimental approaches used to confirm that changes have taken place in the desired way.

1. Introduction

For many years IGF-I was considered a cyto-protective factor for all type of cells in almost every tissue. Therefore, this hormone was broadly considered as beneficial for health. After epidemiological data indicated that blood levels of IGF-I were positively related to cancer risk (LeRoith and Roberts, 2003), this purported beneficial role turned the opposite way. New therapies in cancer are now relying on developing IGF-I receptor antagonists (Tao et al., 2007). Along this detrimental role of IGF-I another line of evidence from genetic studies in aging indicated that the insulin/IGF-I pathway shortens life-span (Kenyon, 2001). Hence, the idea that the general physiological action of IGF-I is detrimental for health is gaining acceptance. Nowadays it is undisputed that reduced insulin/IGF-I effects will result in prolonged life not only in primitive organisms such as worms (Kenyon, 2001) but also in mammals (Holzenberger et al., 2003), including humans (Suh et al., 2008). This is reinforced by the fact that in invertebrate species with a divergent evolutionary history, such as flies, this pathway is similarly detrimental (Clancy et al., 2001). It is probably in the specific case of the aging brain where this detrimental role of IGF-I may be challenged. Indeed, the neuroprotective actions of IGF-I encompass the aging brain and related diseases (Trejo et al., 2004a). Based only in the amount of information, evidence portraying IGF-I as a wide spectrum neuroprotective agent greatly outweighs observations documenting the opposite.

2. IGF-I as a neuroprotective factor

The role of IGF-I in regulating brain growth during development was firmly established through classical genetic manipulation using overexpression and deletion of this growth factor in transgenic mice. The absence of IGF-I is perinatally lethal but the few surviving animals show pronounced microcephaly and many brain abnormalities (Vicario-Abejon et al., 2003; Baker et al., 1993). Conversely, overproduction of IGF-I leads to organomegaly affecting specific organs such as the brain (D'Ercole et al., 1996). In the latter, a general overgrowth effect was observed, although the myelin content was specifically increased.

In the adult brain, IGF-I is an important signal in brain homeostasis. The number of beneficial actions exerted by IGF-I is constantly growing. IGF-I promotes tissue remodelling by controlling the formation of new neurons, vessels and myelin in the adult brain (Torres-Aleman, 2010). IGF-I participates in brain metabolism in ways that are not fully understood but that appear essential to metabolic homeostasis (Bondy and Cheng, 2002). This growth factor directly affects higher brain functions through an array of actions on neurons, glia and the rest of cells that constitute brain tissue. In this way, IGF-I has shown prominent effects on cognition by its underlying actions at the level of neurotransmission, neuronal excitability, and synaptic plasticity (reviewed in (Aleman and Torres-Aleman, 2009). For these

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reasons, IGF-I is currently considered a prototype neuroprotective factor in the adult brain (Trejo et al., 2004a).

3. IGF-I neuroprotection in the aging brain

In mammals, levels of IGF-I decrease with age. In humans this decrease starts relatively early, at the third decade of life. Whether this decrease is adaptive or merely reflects a general tissue decay is not known. At any rate, administration of IGF-I has shown widely neuroprotective actions in the aging brain. Namely, IGF-I improves learning and memory (Markowska et al., 1998), synaptic plasticity (Sonntag et al., 2000) or vascular growth (Sonntag et al., 1997), while diminishes oxidative stress in brain tissue (Puche et al., 2008). In elderly humans, serum IGF-I levels positively correlate with cognitive status (Aleman et al., 1999), and a similar correlation in mice unveiled a trophic action of circulating IGF-I on glutamate neurotransmission affecting synaptic plasticity and cognition (Trejo et al., 2007). Indeed, all major derangements commonly found in the aging brain, including cell atrophy/dysfunction, metabolic impairment, altered higher brain functions and accumulation of deleterious substances can be ascribed to reduced brain IGF-I input, a condition that is inherently linked to the aging process (Trejo et al., 2004b). Thus, lower IGF-I levels as individuals age are coupled to reduced sensitivity to this growth factor.

In this vein, as age-associated brain pathologies may be related to an exacerbated loss of IGF-I input (Trejo et al., 2004a), replacement therapy has shown promising effects in a number of neurodegenerative diseases (Torres-Aleman, 2007), most prominently in animal models of Alzheimer's disease (Carro et al., 2002, 2006), the most common type of neurodegeneration associated with aging. Clinical data have also reinforced a possible role of IGF-I in this disease. Thus, increased levels of serum IGF-I have been reported in early stages of AD, while at later stages serum IGF-I levels are low (Vardy et al., 2007; Watanabe et al., 2005). This agrees with the notion that circulating IGF-I levels will be increased in the initial stages of AD as a result of an ongoing resistance process while at later stages the levels of this serum growth factor would be decreased due to depletion of tissue resources (Carro and Torres-Aleman, 2004). Moreover, diverse drugs currently on the market, such as donepezil and glatiramer acetate (Butovsky et al., 2006; Tei et al., 2007), together with novel compounds still in clinical trials (Bolos et al., 2010), display IGF-I-increasing effects. Recently, IGF-I levels have been proposed as a biomarker to predict therapeutic responses to donepezil in AD (Yamagata et al., 2010). In addition, a biomarker protein array recently described for AD includes insulin-like binding protein 6, a carrier protein for IGF-I (Ray et al., 2007).

Conversely, clinical trials with ghrelin agonists that stimulate growth hormone and in this way raise serum IGF-I levels have shown no efficacy in AD patients (Sevigny et al., 2008). Moreover, other authors failed to replicate the beneficial actions of IGF-I in animal models of AD-related amyloidosis (Lanz et al., 2007). Finally, recent publications concluded that genetic reduction of IGF-I/insulin signalling protects against AD-like pathology in animal models of the disease (Cohen et al., 2009; Freude et al., 2009; Killick et al., 2009).

4. The controversy on the role of IGF-I in the aging brain: the case of Alzheimer's dementia

Alzheimer's disease (AD) is the most common type of disturbance in the human aging brain. That previous evidence from animal models suggested that IGF-I could be of therapeutic use in AD (Carro et al., 2002, 2006), while more recent observations indicate that inhibition of IGF-I could equally be beneficial in AD (Cohen et al., 2009; Freude et al., 2009; Killick et al., 2009) exemplifies the confusing situation of the field (Fig. 1). Presently, these opposing views are difficult to reconcile. Thus, administration of either IGF-I receptor antagonists, currently in clinical trials for various cancers (Tao et al., 2007), or administration of IGF-I or its mimetics, would both seem a logical pursuit for treatment of AD based on these disparate observations. However, fueled by these apparently irreconcilable views, new research will hopefully lead to a better understanding of the significance of this growth factor in AD and in brain aging in general. Until new data becomes available several issues merit further discussion.

The first intriguing fact is that the controversy arises from data gathered using differing experimental approaches. Detrimental actions of IGF-I in the brain have been found after genetic ablation of either the IGF-I receptor or its downstream docking protein IRS-2. Conversely, all the beneficial actions of IGF-I have been reported after administration of the peptide to various animal models. Maybe the different approaches used explain the opposite results. While the underlying assumption of reducing IGF-I receptor is that the biological action of this pathway will be consequently reduced in the brain, and that administration of IGF-I will lead to the opposite effect, the authors of the different studies did not provide direct evidence that the intended changes were taking

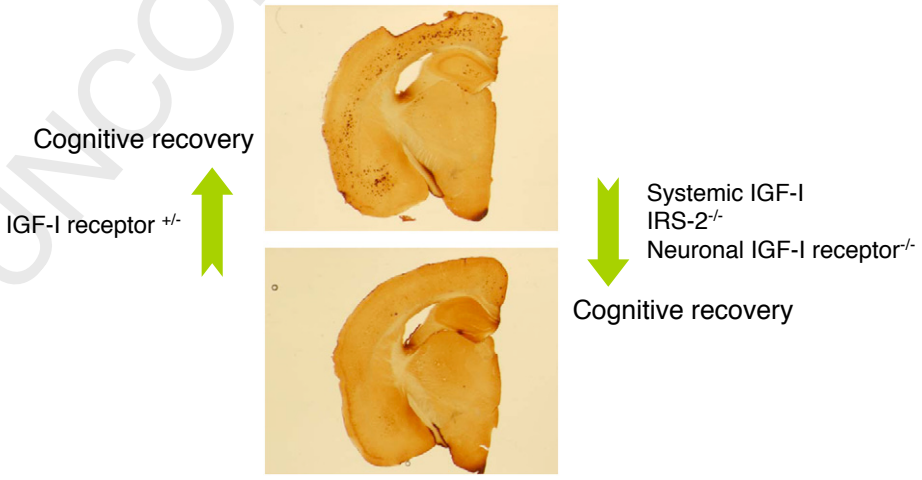

Fig. 1. Cognitive deficits in the animal models of Alzheimer's amyloidosis are corrected by manipulation of IIS signalling in differing and even opposite ways. Subcutaneous administration of IGF-I to transgenic mice overexpressing Aβ peptides reduces plaque load, gliosis and restores cognition (Carro et al., 2006). Similar results are obtained after crossing IRS-2 knockouts with Aβ-overproducing mice, although in this case animals displayed aberrant tau phosphorylation (Killick et al., 2009; Freude et al., 2009). Cross-breeding of Aβ-overproducing mice with neuronal IGF-I receptor knockouts also reduces plaque load and improves cognition (Freude et al., 2009). When IGF-I receptor heterozygous knockouts are bred with Aβ-overproducing mice, plaque size is increased but cognition is restored and neuronal loss mitigated (Cohen et al., 2009).

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place. More importantly, other unaccounted changes may occur, particularly when using knockout mice where the targeted deletion may produce pleiotropic effects along development. Another intriguing point is that both IRS-2 and neuronal IGF-I receptor knockouts present cognitive disturbances (unpublished observations) while after crossing them with Aβ-producing mice, cognitive disturbances present in both strains appear corrected.

An attempt to reconcile both observations was to suggest that increasing IGF-I levels will result in downregulation of brain IGF-I signaling (Cohen et al., 2009). This idea has not yet been tested, but the absence of neuronal IGF-I receptors is accompanied by increased serum IGF-I levels in mutant mice (Kappeler et al., 2008), suggesting that an opposite relationship between brain IGF-I receptors and serum IGF-I may exist. If this is the case, then low serum IGF-I levels, as seen in aged individuals, would result in higher IGF-I receptor function in the aging brain. However, IGF-I receptor function is reduced in the aging brain even though serum IGF-I levels are also reduced (Muller et al., submitted). This is not surprising as both IGF-I deficiency and resistance to IGF-I are associated to aging in other tissues (Trejo et al., 2004b). Thus, available evidence suggest that this apparent opposite relationship between serum IGF-I levels and brain IGF-I receptors is not always present. Furthermore, reduced serum IGF-I levels do not result in reduced brain IGF-I levels (Adams et al., 2009), suggesting that both compartments are regulated independently. It is clear then that the relationship between systemic and brain IGF-I function is complex, forbidding any preconceptions. Hence, experimental approaches aimed to either increase or decrease brain IGF-I function need to firmly establish that the intended changed is obtained. Namely, when either reducing IGF-I receptors/downstream molecules or administering IGF-I, brain IGF-I function needs to be assessed from a functional perspective, such as measuring Akt activation, a canonical pathway downstream of the IGF-I receptor.

Other non-exclusive possibilities may be envisaged. Thus, it is possible, as recently documented for BDNF (Ji et al., 2010), that distinct cellular responses to IGF-I may be triggered depending on the way this pathway is activated. That is, chronic reduction of IGF-I signalling in IGF-I receptor mutants or IRS-2 knockouts may not necessarily lead to reduced IGF-I activity as we currently know from acute exposure of cells to this growth factor. Rather, a distinct, an as yet unknown type of cellular response to prolonged activation of this pathway may be disrupted. Furthermore, administration of IGF-I may elicit cell/tissue responses that are not necessarily the opposite of those seen in heterozygous IGF-I receptor KOs, as recently suggested (Cohen et al., 2009). Thus, reduction/deletion of brain IGF-I receptors may elicit compensatory responses in related systems (i.e.: brain insulin receptors) or address other functions of this receptor that are currently poorly characterized, such as its role in APP metabolism.

5. Conclusions

In the face of declining IGF-I function with age, administration of IGF-I has proven widely beneficial to the aging brain. However, a wealth of evidence indicates that IGF-I is deleterious for aging. In addition, the neuroprotective effects of IGF-I have also been challenged in relation to Alzheimer's disease. The current controversy witnesses our incomplete understanding of the role of insulin and insulin-like peptides in the aging brain and emphasizes the urgent need to undertake new directions in the field.

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