J Mol Med (2004) 82:156–162
DOI 10.1007/s00109-003-0499-7

REVIEW

José Luis Trejo · Eva Carro · Eva Garcia-Galloway · Ignacio Torres-Aleman

Role of insulin-like growth factor I signaling in neurodegenerative diseases

Received: 24 June 2003 / Accepted: 30 September 2003 / Published online: 28 November 2003

Abstract Disturbed trophic support to neurons has long been considered a potential mechanism in neurodegeneration. Recent evidence indicates that intracellular trophic signaling may be compromised in several neurodegenerative diseases. Changes in the levels of insulin-like growth factor I (IGF-I), a trophic hormone with multiple neuroprotective actions, have recently been observed in several human neurodegenerative illnesses. Therefore analysis of IGF-I pathways could help provide greater insight into trophic disturbances to neurons. However, neurodegenerative diseases with similar clinical manifestations show either high or low levels of circulating IGF-I. This apparently puzzling observation can be explained if we consider that IGF-I input to target neurons is disrupted by either lower IGF-I availability or by reduced cell sensitivity to IGF-I. The latter disturbance may be associated with high IGF-I levels. We hypothesize that in the majority of neurodegenerative diseases compromised IGF-I support to neurons emerges as part of the pathological cascade during the degenerative process and contributes to neuronal demise. In addition, loss of IGF-I input to specific neuronal populations might be the cause of a small group of neurodegenerative diseases.

Keywords Insulin-like growth factor · Intracellular trophic signaling · Neurodegenerative diseases

Abbreviations *AT:* Ataxia-telangectasia · *Aβ:* Amyloid-β · *IGF:* Insulin-like growth factor · *IGFBP:* Insulin-like growth factors binding protein · *IRS:* Insulin receptor substrate protein · *LID:* Liver IGF-1 deficiency · *SCA:* Spinocerebellar ataxia · *TNF:* Tumor necrosis factor

José L. Trejo obtained his Ph.D. degree at the Department of Cellular Biology, Universidad Complutense de Madrid, Spain, in 1997. He currently works at the Cajal Institute, Madrid, as a postdoctoral fellow. His main interests are the neurogenesis in the adult hippocampus and the mechanisms of neuroprotection and brain repair mediated by IGF-I.

Ignacio Torres-Aleman received his Ph.D. degree in biology from Complutense University, Madrid, Spain. He is presently Professor of the Spanish Research Council and director of a laboratory in the Cajal Institute of Madrid. His research interests include the role of IGF-I in the brain and its impact on neurodegenerative diseases.

J. L. Trejo · E. Carro · E. Garcia-Galloway · I. Torres-Aleman (✉)
Laboratory of Neuroendocrinology, Instituto Cajal,
CSIC,Avda. Dr. Arce 37, 28002 Madrid, Spain
e-mail: torres@cajal.csic.es
Tel.: +34-91-5854729, Fax: +34-91-5854754

Introduction

A network of trophic relationships maintain neurons alive not only during development but also in adult life. A constantly increasing number of humoral growth factors known to be active in different tissues are now considered to participate also in brain physiology. While recognized for decades as neuroactive, insulin and its relatives insulin-like growth factors (IGFs) I and II had not been categorized as neurotrophic peptides due to their metabolic actions. Probably not until as recently as 1997, when Greenberg and colleagues [1] described the action of IGF-I as a prototypical neuronal-survival factor were these peptides accepted as bona fide neurotrophic signals. This conceptually new scenario eventually led to the sugges-

tion that insulin-like peptides are important determinants of neuronal health and disease [2, 3].

The IGFs are found in ancient organisms, before the vertebrate/invertebrate dichotomy occurred. In the nematode *Caenorhabditis elegans* up to 32 different members of this family have been cloned [4]. In mammals three IGFs have been isolated together with up to four more distant members, the relaxin peptides. Only insulin and IGF-I are characterized as neurotrophic, while the role of IGF-II in the brain and elsewhere is less established. Together with at least ten IGF binding proteins (IGFBPs) of varying affinity and three or four membrane receptors that bind the ligands of the family with differing affinity the IGFs constitute a remarkably complex trophic system. While insulin actions in the adult seem to be mostly, if not entirely, related to metabolic control, IGF-I is a pleitropic hormone, with an extraordinary variety of effects on target organs. Although pleiotropism is a trait of many growth factors, the actions of IGF-I on the brain are particularly varied. At the cellular level IGF-I is best described as a prosurvival factor, generally acting through the phosphatidylinositol 3-kinase/Akt pathway to activate antiapoptotic cascades [5]. However, IGF-I also enhances nerve cell metabolism [6] and modulates neuronal excitability [7], two properties that together with its antiapoptotic actions may be crucial in the ability of IGF-I to protect nerve cells against insults [8]. At tissue level IGF-I stimulates vessel formation [9], regulates amyloid load [10], and modulates the activity of neuronal circuitries [11, 12]. Based on these biological activities it is plausible that changes in IGF-I input to the brain underlie or at least contribute to the progress of neurodegenerative processes. In the present work we analyze the significance of IGF-I signaling to brain cells and outline mechanisms that may lead to impaired IGF-I input to neurons.

Regulation of IGF-I signaling

Although IGF-I can interact with insulin and IGF-II receptors, at physiological levels it binds to the type I IGF tyrosine-kinase membrane receptor. Binding to the IGF-I receptor is modulated by the IGFBPs because the affinity of IGF-I for its carrier proteins is greater than for its own receptor [13]. By controlling IGF-I availability to target cells the IGFBPs probably constitute crucial modulators of IGF-I signaling. Further control of IGF-I signaling is provided by regulation of IGF-I binding to the IGFBPs through degradation, phosphorylation or binding to partners located in the extracellular milieu [14]. Therefore at least two sequential regulatory systems operating prior to IGF-I binding to its receptor modulate IGF-I signaling (Fig. 1). Once IGF-I interacts with its receptor, intracellular signaling progresses through a cascade of kinase activation and protein-protein interactions initially triggered by in *trans*-autophosphorylation of the IGF-I receptor [15]. Through recruitment of insulin receptor substrate proteins (IRSs) and other docking partners

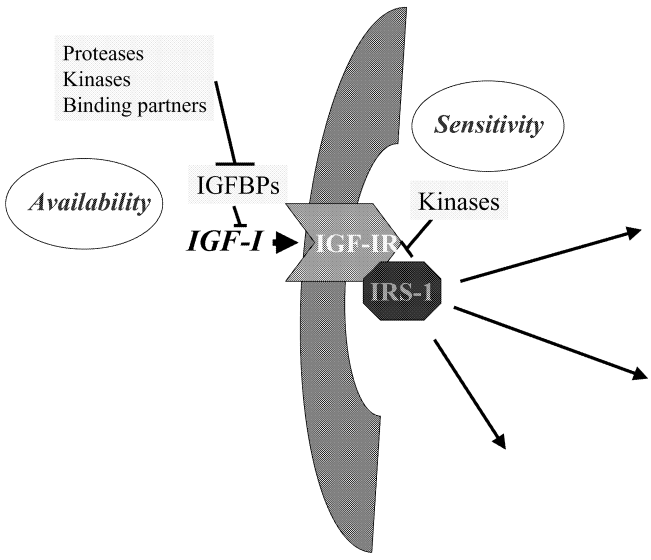

Fig. 1 IGF-I input to target cells depend on IGF-I availability and on cell sensitivity to IGF-I. A greater affinity for the IGFBPs together with their relative abundance originates that the bulk of IGF-I binds to IGFBPs. IGF-I becomes available to target cells ("free" IGF-I) by regulated release from the IGFBPs. The latter lose affinity for IGF-I by specific protease cleavage, phosphorylation or binding to alternative partners in the extracellular milieu. In turn, downstream signaling by the IGF-I receptor can be potentially modulated at multiple steps. A major regulatory checkpoint may be the interaction between IRS and the activated IGF-I receptor. Multiple phosphorylation sites in the IRS protein make it suitable to modulation of its binding to the IGF-I receptor by different kinases. In most cases ser-phosphorylation of IRS results in uncoupling to the activated IGF-I receptor which leads to cell resistance to IGF-I

downstream signaling diverges in a cell-type and cell-context dependent manner. Within the cell, control of IGF-I signaling can potentially take place at so many different steps that is beyond the scope of this review to discuss them. Nevertheless, one well described regulated step is the coupling of IRS with the phosphorylated IGF-I receptor. Different extracellular and intracellular signals modulate the interaction of IRS with the IGF-I receptor (Fig. 1). In most cases phosphorylation of IRS on serine residues results in its uncoupling to the activated IGF-I receptor [16]. Because IRS contains dozens of potential phosphorylation sites [17], kinase regulation of this docking protein is likely very complex.

At any rate, the existence of these regulatory mechanisms indicates that IGF-I signaling can either be potentiated, diminished, or even abrogated by ligand-independent processes. Therefore changes in IGF-I signaling on target cells depend not only on changes in IGF-I levels but also on IGF-I bioavailability and on cell sensitivity to IGF-I receptor activation (Fig. 1). In the latter case the best documented regulatory processes usually induce loss of sensitivity to IGF-I, i.e., cell resistance to IGF-I, although potentiation of the responses to IGF-I is also known to occur [18].

Table 1 Serum IGF-I and insulin levels in human neurodegenerative diseases (= unchanged levels, – not determined)

Disease	IGF-I	Insulin	Reference
Alzheimer's disease[a]	↑↓	↑	[48, 49]
Stroke	↓	–	[50]
Cerebellar ataxia[b]	↓	↓	[51]
Charcot-Marie-Tooth	↑	=	[19]
Ataxia-telangectasia	↑	↑	[19]
Multiple sclerosis	=	↓	[52]
Amyotrophic lateral sclerosis	↓	↓	[52]
Depressive illness	↑	–	[53]
Spinal cord injury[c]	↓	–	[54]

[a] Increased in late-onset Alzheimer and decreased in familial type
[b] Includes several forms of inherited and sporadic ataxia
[c] Changes are seen in 34% of injured patients

IGF-I signaling in neurodegenerative diseases

Serum and brain IGF-I levels change in several neurodegenerative conditions both in humans and in animal models [19]. As already discussed in detail [8], it is possible that serum IGF-I levels are modified in brain diseases because brain and serum levels of this trophic hormone are functionally interconnected. Since circulating IGF-I crosses the blood-brain barriers [7], changes in brain IGF-I levels may be due to changes in serum levels.

While the pathogenic significance of changes in IGF-I levels remain to be established (see below) it is intriguing that in widely different diseases serum IGF-I levels are altered (Table 1). Because IGF-I is an important prosurvival signal in developing neurons, it is conceivable that it plays a similar role in the adult brain. Accordingly, when a pathological condition develops, IGF-I levels increase to protect affected neurons. This is a distinct possibility supported by the fact that serum IGF-I is neuroprotective for the adult brain. As discussed in detail elsewhere [8], normal levels of serum IGF-I are required to maintain a broad range of brain functions. These include modulation of house-keeping processes involved in energy supply to brain cells, formation of new neurons [47] and vessels, clearance of potentially toxic brain amyloid-β(Aβ), stimulation of neuronal excitability, regulation of synaptic plasticity mechanisms such as long-term depression and long-term potentiation, and even modulation of cognition. Indirect support to the notion that IGF-I is neuroprotective is provided by the observation that the ser-kinase Akt that forms part of the canonical IGF-I prosurvival signaling pathway is altered in neurodegenerative diseases such as spinocerebellar ataxia (SCA) 1 and Huntington's disease [20, 21]. In this context, IGF-I changes adapt to an underlying pathological derangement.

However, this interpretation does not explain why in some types of neurodegenerative diseases IGF-I levels in serum are low while in other types, even with similar clinical phenotype, IGF-I levels are high [19].

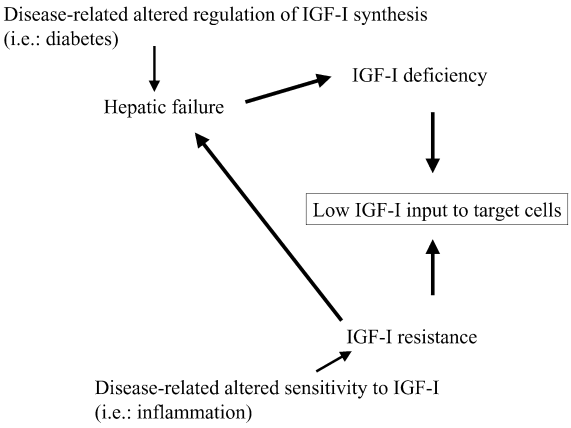

Fig. 2 Mechanisms that may cause low IGF-I input. Low IGF-I levels may originate either from a primary defect in synthesizing organs (exemplified by the liver, the major producer of IGF-I in mammals) or from dysregulation in the synthesis of IGF-I due to the underlying disease; for instance, diabetes leads to low circulating IGF-I due to metabolic/hormonal dysregulation of hepatic function. IGF-I resistance translates into low IGF-I input to cells. Resistance may originate from a primary defect in the IGF-I receptor signaling pathway, for example, due to low levels of IGF-I receptor. Loss of sensitivity to IGF-I may also originate secondary to pathological processes such as inflammation. By triggering a compensatory increase in IGF-I output by synthesizing organs (here exemplified by the liver) IGF-I resistance may eventually lead to cell exhaustion and consequently cause a secondary IGF-I deficiency, which coupled to cell resistance to IGF-I aggravates the process

Mechanisms of IGF-I deficiency

Although IGF-I is produced by many cell types throughout the body, including the brain [22], the principal source of circulating IGF-I is the liver [23]. Therefore a major suspect in serum IGF-I deficiency is hepatic failure (Fig. 2). Hepatocytes may synthesize lower amounts of IGF-I due to direct cellular damage or to dysregulation of IGF-I synthesis. Regardless of the pathogenic trigger, low IGF-I output by the liver results in low trophic input to brain cells because circulating IGF-I enters into the brain [7]. If IGF-I is needed to maintain neuronal health, low input leads to increased neuronal susceptibility to damage. Indeed, mutant mice with very low serum IGF-I due to genetic ablation of the liver IGF-I gene (liver IGF-1 deficiency, LID, mice) show significantly increased damaged hippocampal function after neurotoxic injury. Performance in the water-maze test, a measure of hippocampal-dependent spatial learning, was significantly more impaired after domoic acid insult in LID mice than in control littermates (Fig. 3). Notably, increased susceptibility to damage in LID mice was corrected by treatment with systemic IGF-I (Fig. 3), reinforcing the notion that blood-borne IGF-I input to the brain is important to protect neurons against pathological changes.

It is also possible that IGF-I deficiency develops as a result of a prolonged increased demand of this trophic factor by damaged brain cells. In response to insult brain cells may signal the liver (and other peripheral sources of

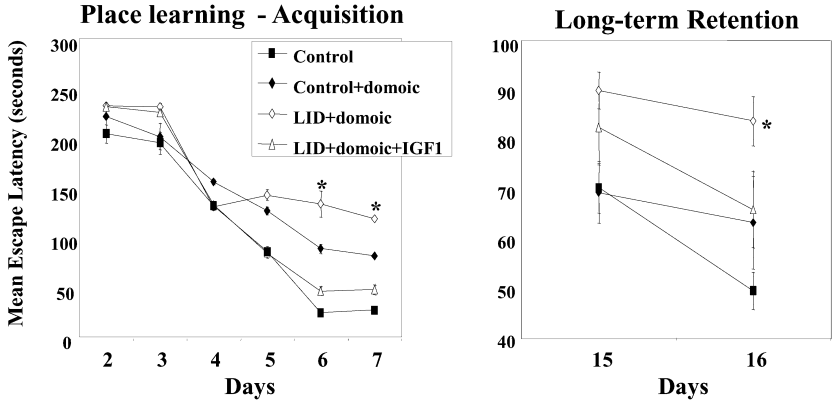

Fig. 3 Serum IGF-I deficiency increases brain susceptibility to injury. Mutant mice with low circulating levels of IGF-I due to genetic ablation of the liver IGF-I gene (*LID* mice) show a significantly greater deficit in hippocampal-dependent spatial learning than control littermates. Injection of domoic acid (0.5 mg/kg, intraperitoneally), an excitotoxic toxin that kills hippocampal neurons produces learning deficits in the water-maze test, a paradigm that assesses the ability of the animal to learn and remember the place of a hidden platform in a water bath. In control littermates deficits are manifest in the acquisition process while retrieval is not significantly affected (*right*). In LID mice both acquisition and retrieval are significantly worse than in controls. Notably, treatment for 2 weeks with systemic IGF-I prior to domoic acid insult significantly protects LID mice against the deleterious effects of the toxin. *P<0.05 vs. control + domoic acid

IGF-I) to increase IGF-I synthesis in order to enhance neuroprotection. As in type 2 diabetes, where pancreatic β cells eventually fail to produce insulin, hepatocytes may also exhaust and fail to keep producing IGF-I as required (Fig. 2).

Mechanisms leading to high IGF-I levels

Trophic loops incorporate a feed-back process whereby input is regulated in accordance to changing demands. When target cells become less sensitive to a given extracellular factor due to loss of receptors or receptor malfunction, a common physiological response is to increase the levels of the given factor. Under pathological conditions nerve cells may become less sensitive to IGF-I through diverse processes, and therefore a compensatory increase in IGF-I levels may be mounted. Indeed, brain levels of IGF-I are usually increased in lesioned areas [24].

At least two pathological processes associated with neurodegeneration can lead to IGF-I resistance in the brain. One is inflammation, a common trait in neurodegenerative diseases [25]. Since proinflammatory cytokines such as tumor necrosis factor (TNF) α attenuate insulin/IGF-I signaling by interfering with IRS coupling to the insulin/IGF-I receptor [26], nerve cells in areas undergoing an inflammatory process may become IGF-I resistant (Fig. 4). Hence not only local but also circulating IGF-I levels could be increased after central nervous system inflammation in an attempt to maintain IGF-I input to the lesioned area. The pathological cascade may be aggravated by impaired passage of serum IGF-I into the brain due to altered brain barrier function. While IGF-I crosses the blood-brain barriers [7], at least in the choroid plexus barrier TNF-α attenuates IGF-I signaling

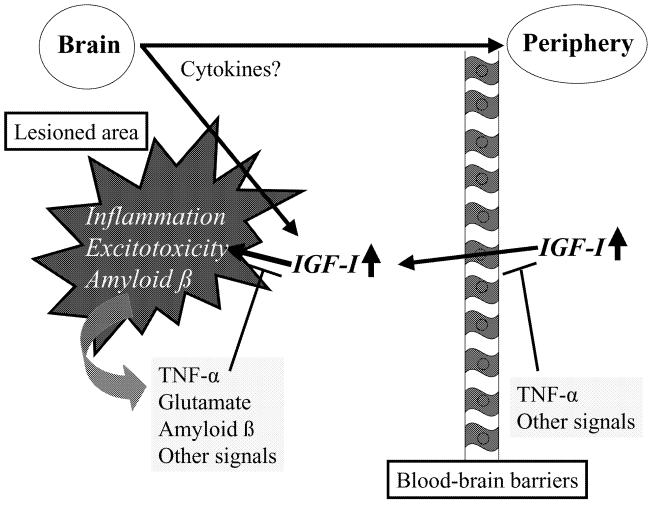

Fig. 4 Factors contributing to development of brain resistance to IGF-I. In neurodegenerative conditions in which inflammation, excitotoxicity, or extracellular accumulation of amyloid (Alzheimer's disease, vascular amyloidosis) occur, loss of sensitivity to IGF-I in the neurons located in the lesioned site may be expected through the antagonistic effects of proinflammatory cytokines (TNF-α), glutamate, or amyloid on IGF-I signaling. Local resistance to IGF-I causes increased IGF-I in the lesioned area as a compensatory mechanism. For this compensatory increase to occur the lesioned brain must signal to the vicinity of the lesion and probably also to the periphery to increase IGF-I input to the lesion. Cytokines are probably these humoral signals because they are produced by cells in the lesion and are involved in multiple reactive processes. Increased IGF-I in the lesioned site is due to increased local synthesis and/or accumulation and to increased peripheral entrance because systemic IGF-I can reach the brain by crossing the brain barriers [7]. Passage of serum IGF-I through the barriers may be in turn diminished by the antagonistic actions of humoral signals such as TNF-α on the barriers [10]. Coupled with resistance to IGF-I in the lesioned area, the resulting lower IGF-I input from the periphery into the brain aggravates the process

[10]. A similar situation may develop in excitotoxic damage. Overstimulation of neuronal excitatory signaling through excess glutamate underlies several important neurodegenerative processes [27]. Because excitotoxic, but not normal, doses of glutamate attenuate IGF-I signaling in vitro and in vivo [28], neurons located in the vicinity ("penumbra") of the excitotoxic lesion lose sensitivity to IGF-I. A further and intriguing possibility is that extracellular accumulation of Aβ causes cell resistance to IGF-I. In this case the mechanism leading to loss of sensitivity to IGF-I would be related to the ability of Aβ to bind to the IGF-I receptor as a competitive antagonist. Aβ antagonizes the insulin receptor [29]. Since the insulin receptor is very similar in binding requirements to the IGF-I receptor [30], it is quite probable that Aβ competes also with IGF-I binding. At any rate, the reported development of insulin resistance in Alzheimer's brains [3] is very likely associated with brain IGF-I resistance [31]. Consequently, in neurodegenerative conditions in which inflammation, excitotoxicity, and extracellular accumulation of Aβ take place we may expect an increase in IGF-I levels in the lesioned site. Indeed, reactive glial cells associated with brain lesions usually present high levels of IGF-I. This increase may originate from enhanced local synthesis/accumulation of IGF-I and/or increased IGF-I input from peripheral sources.

This scenario requires the existence of brain signaling not only to the penumbra of the lesion but to peripheral organs such as the liver to upregulate IGF-I levels (Fig. 4). What are the brain-derived signal(s) that modulate IGF-I synthesis on demand? Because these hypothetical signals should be associated with the lesion, humoral factors such as cytokines are possible candidates. Cytokine signaling orchestrates the immune response to neuronal damage [32] and modulates the synthesis of IGF-I and its binding proteins by peripheral organs [33, 34, 35]. In turn, IGF-I is an immune modulator and participates in the inflammatory response [36]; therefore a regulatory loop encompassing cytokines and IGF-I seems plausible.

Pathogenic relevance of IGF-I resistance and IGF-I deficiency in neurodegenerative diseases

Altered IGF-I input may either be the primary cause of neuronal damage (pathway 1 in Fig. 5) or develop as a consequence of neuronal damage (pathway 2). We consider that the two possibilities can take place according to the type of disease. For instance, primary disturbances in IGF-I synthesis in the liver due to hepatic damage, diabetes, or other conditions cause low IGF-I levels that eventually may lead to neurological impairments as seen in hepatic encephalopathy or diabetes. For the latter disease it is well documented that serum IGF-I levels decrease, and that replacement therapy with IGF-I ameliorates diabetic neuropathy [37]. In turn, reduced neuronal sensitivity to IGF-I following inflammation [26] or excitotoxic insult [28], as discussed above, may contribute to cell death in these conditions. Therefore we may distinguish conditions in which IGF-I failure is the origin of neuronal dysfunction/death from those where it contributes to the disease. We speculate that the latter situation is the most common because inflammation and excitotoxicity are usually associated with neuronal death.

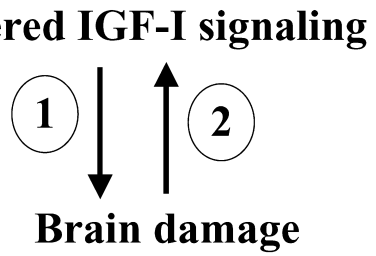

Fig. 5 Hierarchical relationship between IGF-I signaling and brain disease. Altered IGF-I signaling may cause brain damage (*1*) or, alternatively, develop as a consequence of it (*2*). Diseases such as ataxia-telangectasia, dentatorubral-pallidoluysian atrophy, spinocerebellar ataxia 1, and Huntington's disease may potentially be included in the former case. Age-related diseases such as late-onset Alzheimer's disease may also be due to low IGF-I signaling. However, in most neurodegenerative diseases disrupted IGF-I signaling may be a consequence of prior brain damage. In the first case IGF-I dysfunction can be considered etiopathogenic while in the second case as an additional pathological process contributing to the pathological cascade

Altered IGF-I signaling as the cause of neurodegenerative diseases

Several relatively rare neurodegenerative diseases may be due to low IGF-I input to neurons. These include ataxia-telangectasia (AT), in which low levels of IGF-I receptor, apparently caused by mutation of the affected protein, lead to loss of sensitivity to IGF-I in fibroblasts [38]. This loss of cellular sensitivity to IGF-I is likely also found in the rest of IGF-I receptor bearing cells of AT patients, including neurons. Indeed, AT patients, who have mutations in Atm, a DNA-kinase of the phosphatidylinositol 3-kinase family, show high serum IGF-I levels [19], a characteristic trait of systemic resistance to IGF-I [31]. Similarly, dentatorubral pallidoluysian atrophy, a triplet repeat disease in which the wild-type but not the mutated protein appears to interact with the IGF-I signaling pathway [39], may also involve loss of IGF-I signaling in affected neurons. Other possible diseases in which a primary defect in IGF-I signaling might be involved include SCA-1 and Huntington's disease where, as noted above, impaired Akt signaling appears as a probable pathogenic mechanism [20, 21]. Although not yet confirmed, it seems that a tonic phosphatidylinositol 3-kinase/Akt-mediated prosurvival signaling is provided by IGF-I in adult neurons.

A pending issue is the disease-specific pattern of cell death seen in neurodegenerative diseases. While several explanations have been proposed to account for this

specificity, the question remains open. If compromised IGF-I input leads to neuronal loss of specific subsets of neurons in AT, dentatorubral pallidoluysian atrophy, SCA-1, Huntington's disease, or other diseases, the most logical explanation is that only the dying cells have an IGF-I signaling dysfunction. However, this is at present entirely speculative. We should determine in animal models of these diseases whether affected neurons specifically lose sensitivity to IGF-I.

Altered IGF-I signaling in the progression of neurodegenerative diseases

It is probable that in many neurodegenerative diseases low IGF-I input to neurons contribute to neuronal death once the pathological cascade has been triggered by either genetic factors, genotype/phenotype interactions, or the environment. For instance, loss of sensitivity to IGF-I may develop secondary not only to inflammation or excitotoxicity, as mentioned above, but can also be induced by prion infection [40], environmental toxins [41], or ethanol consumption [42]. Sequestration of IGF-I by high levels of IGFBPs in lesioned areas, as recently proposed in spinal cord of amyotrophic lateral sclerosis patients [43] may also impede the trophic effects of this peptide. Low circulating levels of IGF-I after hepatic dysregulation in diabetes may underlie not only associated diabetic neuropathies but also the known association with diabetes of different neurodegenerative diseases [44, 45, 46]. Similarly, low serum IGF-I levels associated with aging may underlie age-associated neurodegeneration, including major diseases such as late-onset Alzheimer's disease (Carro and Torres-Aleman, in press).

Taking these findings together, we may conclude that disrupted IGF-I signaling is a common trait in neurodegeneration. By determining the precise site of disruption and the underlying molecular processes new therapeutic targets potentially useful for many types of neuronal death processes may be discovered. For instance, based in our work with IGF-I neuroprotective pathways we have found that protein kinase Cε in ischemia [28], and megalin in Alzheimer's disease [10] may constitute relevant targets in the search for new drugs.

Conclusions

IGF-I exerts important neuroprotective effects in the adult brain. We propose that impaired IGF-I input to neurons as a result of IGF-I deficiency or loss of sensitivity to IGF-I participates in the development and, most frequently, in the progression of neurodegenerative diseases. To determine the validity of our proposal we consider that is essential to measure serum IGF-I levels in all types of neurodegenerative diseases and assess cell sensitivity to IGF-I, for example, using skin fibroblasts from the patients. Additional and feasible clinical tests that would help determine whether IGF-I production is disrupted in the patients may include stimulation of liver IGF-I production with growth hormone and measurement of circulating cytokines. More conclusive, treatment of patients with IGF-I should ameliorate progress of the disease.

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