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The Insulin-Like Growth Factor System and Its Pleiotropic Functions in Brain

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In recent years, much interest has been devoted to defining the role of the IGF system in the nervous system. The ubiquitous IGFs, their cell membrane receptors, and their carrier binding proteins, the IGFBPs, are expressed early in the development of the nervous system and are therefore considered to play a key role in these processes. *In vitro* studies have demonstrated that the IGF system promotes differentiation and proliferation and sustains survival, preventing apoptosis of neuronal and brain derived cells. Furthermore, studies of transgenic mice overexpressing components of the IGF system or mice with disruptions of the same genes have clearly shown that the IGF system plays a key role *in vivo*. (*Endocrine Reviews* 26: 916–943, 2005)

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Abbreviations: Aβ, β-Amyloid peptide; AD, Alzheimer's disease; ALS, amytrophic lateral sclerosis; CNS, central nervous system; CSF, cerebrospinal fluid; EPO, erythropoietin; FGF, fibroblast growth factor; GPE, N-terminal tripeptide (glycine-proline-glutamate); HIF, hypoxia-inducible factor; IGF-IR, type I IGF receptor; IRS, insulin receptor substrate(s); LID, liver-specific IGF-I deficient; MN, motor neuron; M6P, mannose-6 phosphate; NMDA, *N*-methyl-D-aspartate; NSILA, nonsuppressible insulin-like activity; NT, neurotrophin; PI3K, phosphatidylinositol 3-kinase; PRL, prolactin; SOD1, Cu/Zn superoxide dismutase.

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I. Introduction

THE AVAILABILITY OF animal models for brain injury and neuronal degeneration has allowed the investigation of the role of IGF-I in prevention and rescue of damaged neuronal cells. These studies have thus pointed to the potential therapeutic use of IGF-I alone or in combination with other neuroendocrine factors in the treatment of nervous system diseases.

The main aim of this review is therefore to provide an up-to-date and comprehensive analysis of the pleiotropic functions of the IGF system in the nervous tissue. To maintain focus on the IGF system, the role and functions of the insulin system in brain and neuronal cells, also important but already amply reviewed elsewhere, will only be mentioned and discussed in brief in this review.

II. Historical Perspective

In 1957, Salmon and Daughaday (1) reported a serum factor (factors) that mediated the cartilage sulfation and longitudinal bone growth activity of the somatotrophic hormone (GH) (2, 3). This factor was termed "sulfation factor" and was produced by hepatic cells after exposure to GH (1). In conjunction, Dulak and Temin (4) were investigating the cell proliferative factors in serum and termed one such ac-

tivity multiplication-stimulating activity. These circulating factors, which also showed insulin-like activity not suppressible by antiinsulin antibodies [nonsuppressible insulin-like activity (NSILA) I and II] (5–10), were later found to have a similar biochemical structure to the β-chain of insulin (11–13). It was apparent that these activities represented a similar group of substances with a wider biological activity than first suspected (3). NSILA I and II were two forms of an insulin-like hormone with predominant effects on cell and tissue growth (11). These small molecular mass peptides (NSILA I and II) were later renamed as somatomedins replacing the "nonsuppressible insulin-like activity" and sulfation factor terminology. Further investigation revealed that these factors mediated the actions of pituitary-derived GH, giving birth to the somatomedin hypothesis (3).

Shortly thereafter, two mammalian somatomedins were identified by protein sequence and cDNA data (11, 14–18) and their structural homology with proinsulin led to their current designation of IGF-I and IGF-II.

In the middle 1990s, Sara and co-workers (19, 20) identified a brain-specific variant of IGF-I, des(1-3) or "truncated" IGF-I, which lacks the first three amino acids and is more potent than intact IGF-I in various cell culture systems (19–21), probably due to its lower affinity for IGF binding proteins (IGFBPs) (22). This finding suggested brain synthesis of IGF-I or its truncated variant. After the isolation of IGF-I mRNA from postnatal rat brain (23), a number of *in situ* hybridization studies (24, 25) demonstrated that IGF-I and IGF-I receptor mRNA are synthesized in the rat brain in specific regions, namely olfactory bulb, hippocampus, and cerebellum (26). In addition IGF-carrier proteins, later named IGF binding proteins, were also found expressed in similar brain regions (27–36). The finding of IGF-I mRNA colocalization with IGF-I receptors and the presence of IGFBPs suggested a paracrine or autocrine role for IGF-I, potentially modulated by IGFBP, in the developing brain (26, 36–38).

The presence of IGF-I (39) and IGF-I mRNAs (40) in multiple tissues has necessitated the revision of the original somatomedin hypothesis to include both autocrine and paracrine actions of IGF in addition to its classical endocrine aspects.

The somatomedin hypothesis has been recently challenged by several groups employing the liver-specific IGF-I deficient (LID) mice, which have reduced circulating IGF-I and elevated GH (41, 42), and the acid-labile subunit knockout ALSKO mice (43), which have reduced circulating IGF-I and IGFBP-3 but normal GH level. The LID mice, contrary to expectations (altered IGF-I-mediated GH-stimulated growth), showed normal postnatal growth and development (43, 44), whereas the ALSKO mice, despite 65% reduction in circulting IGF-I, demonstrated only 10% reduction in body weight. Interestingly, when the LID mice were crossed with the ALSKO mice (LID + ALSKO) (43), to further affect the GH/IGF-I axis, the LID-ALSKO mice (very low IGF-I and very high GH levels) showed postnatal growth retardation and osteopenia, suggesting that circulating IGF-I is important for postnatal growth and development (44). Although investigations are ongoing in this area, it is accepted at this stage that IGF-I exerts its pleiotropic functions in an endocrine, autocrine, and paracrine fashion.

III. Overview of the IGF System

A. The IGF peptides

IGF-I and -II are growth-promoting peptides, members of a superfamily of related insulin-like hormones that includes insulin and relaxin in the vertebrates and bombyxin, locust insulin-related peptide, and molluscan insulin-like peptide in invertebrates (12, 13, 45–49). However, insulin and IGFs are the most closely related in terms of primary sequence and biological activity. The IGFs are major growth factors, wheras insulin predominantly regulates glucose uptake and cellular metabolism. They consist of A, B, C, and D domains. Large parts of the sequences within the A and B domains are homologous to the α- and β-chain of the human proinsulin. This sequence homology is 43% for IGF-I and 41% for IGF-II. No sequence homology exists between the C domains of IGFs and the C peptide region of human proinsulin. The C domain of the IGFs is not removed during prohormone processing; thus the mature IGF peptides are single chain polypeptides (50, 51). The gene encoding IGF-I is highly conserved (50, 52–56) such that 57 of 70 residues of the mature protein are identical among mammals, birds, and amphibians (50, 52–56). For a more extensive review of structure, functions, and regulation of the IGF-I gene, see Refs. 57–61.

Expression of the *Igf-1* gene is affected at many levels including gene transcription, splicing, translation, and secretion. IGF-I expression is also influenced by hormonal (GH) (1, 62–66), nutritional (67–69), tissue-specific and developmental factors (36, 70–73).

B. The IGF receptors and their functions

The biological actions of the IGFs are mediated by the type I IGF receptor (IGF-IR), a glycoprotein on the cell surface that transmits IGF binding to a highly integrated intracellular signaling system (74–77). Binding of the IGFs (IGF-I and II) to the IGF-IR (74, 78–84) promotes intrinsic tyrosine kinase activity that phosphorylates the insulin receptor substrates (IRS-1 to IRS-4), which then leads to the activation of two main downstream signaling cascades, the MAPK and the phosphatidylinositol 3-kinase (PI3K) cascades (85–90). However, IGF-II binds the IGF-IR with lower affinity (74, 78–84). Expression of the IGF-IR gene (77, 91) has been detected in many tissues and is constitutively expressed in most cells (92–94); its promoter is regulated *in vitro* and *in vivo* by transcription factors such as SP1 (95, 96) and the transcription factor p53 (97, 98).

Various IGF-I receptor subtypes that present distinct structures or binding properties have also been described. Two of these subtypes, namely hybrid and atypical IGF-I receptors, have been particularly investigated in a variety of cell types (99–102). The atypical IGF receptors are characterized by their ability to bind insulin as well as IGFs with relatively high affinity (103). Hybrid insulin/IGF-I receptors have been reported in cells expressing both IGF-I and insulin receptors (104–108); however, the physiological significance of hybrid and atypical IGF receptors is unclear.

The IGF-II ligand has greatest affinity for a distinct receptor, the type-II or IGF-II receptor (109–114). This single chain polypeptide with a short cytoplasmic domain lacking ty-

rosine kinase activity is identical to the cation-independent mannose-6 phosphate (M6P) receptor (107, 115, 116). The IGF-II/M6P receptor binds two general classes of ligands: 1) non-M6P-containing ligands, the best characterized of which is IGF-II; and 2) M6P-containing ligands, including lysosomal enzymes. The multifunctional role of the receptor is evidenced by its function in the mediation of lysosomal enzyme trafficking, endocytosis, and lysosomal degradation of extracellular ligands, regulation of apoptotic/mitogenic effects, and possible intracellular signal transduction (115, 117–128).

More recently, high-affinity binding of IGF-II to an insulin receptor isoform (IR-A) has also been reported (129–131), thus suggesting that IGF-II might also signal via the insulin receptor. However, this insulin receptor isoform (IR-A), lacking the alternative spliced exon 11, is preferentially expressed in fetal and cancer cells (130).

C. The IGFBPs

A family of six high-affinity IGF-binding proteins (IGFBP-1 through IGFBP-6) coordinate and regulate the biological activity of IGF in several ways: 1) transport IGF in plasma and control its diffusion and efflux from the vascular space; 2) increase the half-life and regulate clearance of the IGFs; 3) provide specific binding sites for the IGFs in the extracellular and pericellular space; and 4) modulate, inhibit, or facilitate interaction of IGFs with their receptors (111, 132–135). IGFBP biological activity is regulated by posttranslational modifications such as glycosylation and phosphorylation (111) and/or differential localization of the IGFBPs in the pericellular and extracellular space (111, 134–139). It is therefore hypothesized that IGFBPs, in addition to stabilizing and regulating levels of diffusible IGFs, might regulate IGF-I cellular responses by facilitating receptor targeting of IGF-I or modulating IGF-I bioavailability in the pericellular space (111, 135).

The effects of the IGFBPs are further regulated by the presence of specific IGFBP proteases, which cleave the binding proteins, generating fragments with reduced or no binding affinity for the IGFs (111, 135, 136, 140). Some IGFBPs, including IGFBP-2 and -3, can induce direct cellular effects independent of the IGFs (135, 141–144). IGFBP-3, similar to IGFBP-5, contains sequences with the potential for nuclear localization (145, 146) and detection of IGFBP-3 in the nuclei of dividing cells, as reported by several investigators (146, 147), strongly suggesting a role for IGFBP-3 in gene regulation. More recently, perinuclear or nuclear localization has also been reported for IGFBP-2 (148); however, the role of IGFBP-2 in this cellular compartment is yet to be determined.

IV. Expression and Pleiotropic Actions of the IGF System in the Brain

A. IGF expression in the nervous system

Central nervous system (CNS) development begins in the embryo with the formation and closure of the neural tube, followed by the rapid division of pluripotential cells (stem cells), which then migrate to the periphery of the neural tube and differentiate into neural or glial cells. These cells form special structures such as nuclei, ganglia, and cerebral cortical layers, and develop a network with their cytoplasmic extensions, neurites. These complex processes are regulated by a number of growth factors including the IGFs (149, 150).

IGF-I plays a key role in the development of the nervous system, with demonstrated effects on many stages of brain development including cell proliferation, cell differentiation, and cell survival (36, 37, 149–159). Although recent reports have demonstrated that postnatal circulating IGF-I might exert neurogenic/survival activity (160–166) (167–171), systemic IGF-I is not readily transported through the blood-brain-barrier, and therefore local production of IGF-I is considered the primary source of the ligand (autocrine and paracrine action) for brain cells.

During embryogenesis, IGF-I mRNA expression is detectable in many brain regions (23, 25, 31, 172–176), with its expression being particularly high in neuronal rich regions such as the spinal cord, midbrain, cerebral cortex, hippocampus, and olfactory bulb (23, 177, 178) (Fig. 1). More precisely IGF-I is found expressed in neuronal cells with large soma and complex dendritic formations (32, 155), including sensory and projecting neurons such as the Purkinje cells (25). In most neurons, IGF-I transcription decreases significantly postnatally, a decrease that correlates with the degree of cell maturation and reaches very low levels in the adult (23, 175). However, exceptions are the mitral and tufted cells of the olfactory bulb, which undergo constant cell renewal/turnover (179); in these cells IGF-I expression persists at a high level throughout life (26, 179).

IGF-II mRNA is abundantly expressed in the embryonic rat CNS, however data are conflicting on IGF-II expression in cells of neuroepithelial origin (24, 180, 181). IGF-II is the most abundantly expressed IGF in the adult CNS, with the highest level of expression found in myelin sheaths, but also in leptomeninges, microvasculature, and the choroid plexus, all nonneuronal structures that enable diffusion of growth factors to their sites of activity (24, 25, 176, 182–185).

B. Type I and II IGF receptor expression in the nervous system

The IGF receptors are widely expressed throughout the CNS, with high levels of expression found in specific regions and located to specific cell types (25, 26, 36, 38, 119, 153, 186–188). Given that IGF receptors are expressed from early stages of embryogenesis and throughout life, and that their ligands also show similar a "temporal-spatial" pattern of expressions, it is evident that the local brain IGF circuits are crucial modulators of the processes activated during brain development. Type I receptors are expressed throughout the rat CNS (177, 187, 189–191) with high levels of expression detected in the developing cerebellum, midbrain, olfactory bulb (Fig. 1), and in the ventral floorplate of the hindbrain (23, 24, 187). The level of IGF-IR decreases to adult levels soon after birth (192, 193) but remains relatively high in the choroid plexus, meninges, and vascular sheaths (25, 187). It is thus not surprising that knockout of the IGF-I receptor gene (194–196) produced, in addition to *in utero* growth retardation, a strong brain phenotype, namely a small brain.

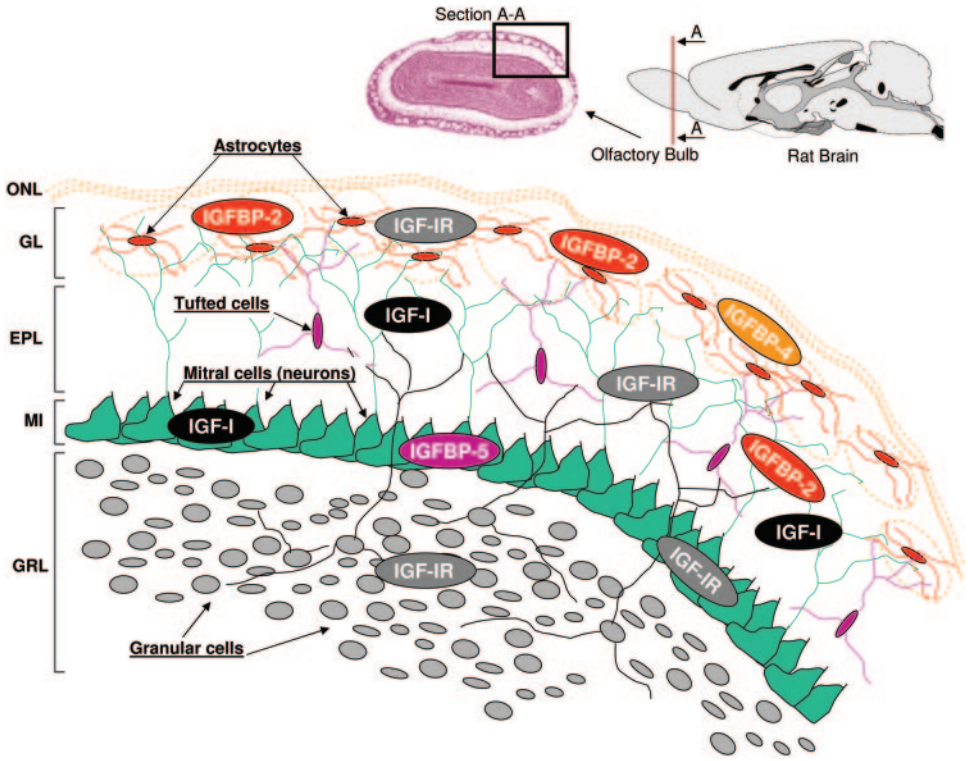

FIG. 1. The IGF system in the rat brain olfactory bulb. IGF-I is expressed and synthesized in distinct areas of the rat brain, adjacent to regions rich in IGF-I receptors and IGFBPs (*i.e.*, olfactory bulb is shown). This provides strong evidence for an autocrine and paracrine action of the IGFs in the nervous system. IGF action is modulated by locally expressed IGFBPs. ONL, Olfactory nerve layer; GL, glomerular cell layer; EPL, external plexiform cell layer; MI, mitral cell layer; GRL, granular cell layer. Section A-A shows a hematoxylin-eosin staining of olfactory bulb. [Modified with permission from L. W. Swanson: Brain Maps: Structures of the Rat Brain, 2nd edition, Elsevier, Amsterdam, 1998/1999 (528).] *Area in the square* is enlarged and represented in the cartoon.

The type II IGF receptor, which has low affinity for IGF-I, but a high affinity for IGF-II, and also binds mannose-6-phosphate, is selectively expressed in all major brain regions (119, 183, 188, 197, 198). It is highly expressed in the pyramidal cell layers of the hippocampus, the granule layer of the dentate gyrus, olfactory bulb, the choroid plexus, and in the cerebral vasculature, ependymal cells, retina, pituitary, brainstem, and spinal cord (119, 183, 188, 197). Some of these regions undergo tissue remodelling, suggesting that the IGF-II/M6P receptor, in addition to its role in transporting lysosomal enzymes, might also participate in control of neuronal growth, differentiation, and repair, processes regulated by IGF-II/M6P receptor ligands including LIF, TGFβ, and retinoic acid (198).

Early studies from our laboratory have demonstrated that some of these regions expressing both the IGF-I and IGF-II receptors are also rich in insulin receptors (199). Insulin receptor density is elevated in the choroid plexus, olfactory bulb, limbic system, and hypothalamus but is much lower in other brain regions (cortex, cerebellum, pituitary gland, thalamus), all regions concerned with olfaction, appetite, and autonomic functions (199). More recently, ablation of the insulin receptor in nestin-positive neurons (NIRKO mouse) (200) suggests a role for insulin in control of appetite suppression and reproduction (200).

C. The IGF ligands are pleiotropic factors

Whether the IGFs are produced locally (23, 25, 31, 172–176, 201) or reach brain cells systemically (160–166), these molecules exert potent neurotrophic, neurogenic, and neuroprotective/antiapoptotic activities. A large number of *in vitro* studies have demonstrated that IGF-I promotes mitogenesis and differentiation in glial cells (202–207), oligodendrocytes (208–210), neuronal cells (36, 37, 211, 212), adult stem cells (213), and brain explants (21, 214–217), and regulates axon myelination (218–220). IGF-I enhances growth cone motility and promotes neurite outgrowth (221, 222).

Studies using the IGF-I $-/-$ mice models (152, 162, 220) have clearly demonstrated that most of the IGF functions determined *in vitro* also apply to the *in vivo* situation, affecting a wide range of brain cells. The IGF-I null mice have reduced brain size and altered brain structures (151, 155) and show alteration of myelination processes (168, 223). This appears to be the result of reduced oligodendrocyte proliferation and maturation, which is also associated with reduction of axonal growth (168, 196, 223). However, some early studies from Bondy and co-workers (220) have reported instead that in IGF-I null mice, myelination is reduced but proportionate to the neuronal composition. Furthermore, ablation of the *Igf-1* gene has revealed deficit in the numbers of specific neurons, oligodendrocytes in the olfactory bulb, dentate gyrus and striatum (194, 196, 220) and in cochlear ganglion neurons (169). These anatomical differences are likely to be the consequences of alteration in proliferation, survival, or differentiation caused by the absence of IGF-I during development. A study from Vicario-Abejon *et al.* (224) suggests that reduction of stem cell proliferation/differentiation in the IGF-I null mice might be the cause of reduced plasticity/maturation normally occuring in some brain regions (*i.e.*, olfactory bulb) postnatally (224). In addition to gross structural brain abnormalities, the IGF null mice also show alteration of important brain metabolic functions such as reduced glucose uptake, the major source of energy of neuronal cells (225). These *in vivo* models thus show that the IGF

system affects several steps involved in development and organization (number of cells, their connection, and the extracellular matrix) of CNS architecture.

However, actions of IGF are not limited to fetal life (25, 149, 150, 226), but extend into postnatal (21, 217) and adult life (185, 227–229), with effects on proliferation, neuronal differentiation, and maturation maintained in some regions of the adult brain. Furthermore, alterations in levels of IGF-I have been reported in the brains of aging rats (230, 231), alterations that also correlate with deterioration of cognitive functions observed in elderly patients with low circulating IGF-I (232–234).

D. The IGFs are neurotrophic factors

In support of studies by the Gluckman group (235) and others on the use of IGFs as therapeutic agents (see also *Section VII*), many investigators have examined the cellular and molecular mechanisms of IGF action in nervous system diseases. In this regard, the IGFs have been shown to be neurotrophic factors, *i.e.*, they promote the survival and differentiation of neuronal cells, including sensory (171, 221, 236), sympathetic (211, 237), and motor neurons (MNs) (236–238). In fact, the IGFs are the only known growth factors that support both sensory and motor nerve regeneration in adult animals (160, 238–243). IGF-I is involved in brain plasticity processes (21, 217, 224, 244), and it specifically modulates synaptic efficacy by regulating synapse formation, neurotransmitter release, and neuronal exicitability (245–248).

IGF-I also provides constant trophic support to neuronal cells in the brain and in this way maintains appropriate neuronal function (245). Alteration of this trophic input may lead to brain disease as seen in neurodegenerative disorders such as Alzheimer's disease (AD) (162, 249), Ataxia telangiectasia (250), Huntington's disease (251), and Parkinson's disease (252), all variably responsive to IGF-I treatment (see also *Section VII*). A recent study by Lichtenwalner *et al.* (253) showed that neurogenesis declines in brains of aged mice, but it is efficiently restored after IGF-I administration via intracerebroventricular infusion.

E. IGF-I prevents neuronal apoptosis

The ability of IGF-I (and IGF-II) to promote neuronal survival is associated with the ability of these factors to prevent apoptosis, and IGF-I appears to be a potent agent for rescuing neurons from apoptosis. For example, IGF-I prevents *N*-methyl-D-aspartate (NMDA)- and nitric oxide-induced apoptosis in hippocampal and cortical neurons (254–258).

IGF-I has been shown to enhance the survival of rat embryo cerebellar granule cells and stimulate their terminal differentiation into cerebellar granule neurons (259, 260). Additionally, IGF-I promotes the survival of rat hypothalamic and hippocampal neurons *in vitro* (261). IGF-I and -II rescue chick MNs from injury-induced and developmentally regulated death (262, 263). A role for IGF-I in the regulation of Schwann cell survival has also been reported (264), as has the ability of IGF-I to prevent apoptosis in sympathetic neurons exposed to high glucose (265). Rat hippocampal neurons are also rescued by IGF-I from the induction of apoptosis by amyloid-derived peptides (162, 266–268). A similar anti-apoptotic effect of IGF-I is observed in rat cerebellar neurons subjected to serum or potassium withdrawal or high KCl levels (269, 270), okadaic acid treatment (271), and in MNs during normal development or (262, 272) after axotomy or spinal transection (273, 274).

Neuroblastoma cells are rescued from hyperosmotic shock-induced apoptosis by IGF-I (275) or metabolic stress (265, 276) including exposure to low glucose (277). IGF-I inhibits mature oligodendrocyte apoptosis during primary demyelination (278) and prevents apoptosis in neurons after nerve growth factor withdrawal (279) or serum withdrawal in brain explants (280) and neuronal cells (281).

F. IGFBP action in the nervous system

A growing body of evidence suggests an important role for IGFBP in the nervous system. The mRNA expression profiles and location of the most abundant IGFBP-2, -4, and -5 in the normal developing and adult CNS are well defined (31–33, 35, 282–284). IGFBP-3 (35, 284, 285) and IGFBP-6 (286) are also discretely expressed in the CNS but at lower levels, and therefore data on their mRNA expression distribution are limited. IGFBP-1 is not expressed in the CNS, but its expression is induced under certain experimental conditions (287).

1. IGFBP-1. Although IGFBP-1 mRNA is normally not detectable in brain and the effects of *Igfbp-1* gene deletion on CNS have not been reported, the overexpression of IGFBP-1 mRNA in brain has instead generated an interesting brain phenotype, namely small brain (288–292).

IGFBP-1 is known to inhibit somatic linear growth, weight gain, tissue growth, and glucose metabolism (293). Increased expression of IGFBP-1 has been documented in a variety of situations, such as fetal nutritional deprivation and hypoxia, and has been considered to be a marker of metabolic disturbances that cause fetal growth retardation. Of interest, IGFBP-1 transgenic mice demonstrate both intrauterine and postnatal growth retardation phenotypes (288–292) including alteration of the somatotrophic axis (294).

In a study by Doublier *et al.* (295), a line of transgenic mice with liver-specific expression of IGFBP-1 also showed impaired brain development and hydrocephalus.

Furthermore, a study by Zhou and co-workers (287) described disrupted cerebellar morphogenesis and reduction in cerebellar size in mice overexpressing the hepatocyte nuclear factor-3β (HNF-3β). The transgenic cerebella displayed levels of IGFBP-1 elevated to 22 times greater than those measured for wild-type cerebella, an elevation consistent with the reduction in transgenic cerebellar size.

Together, these *in vivo* observations suggest that increased expression of IGFBP-1, as observed in a variety of clinical situations, may itself contribute to the growth retardation and impaired fetal brain development. However, it is suggested that the underlying mechanisms in these events involve IGFBP-1-sequestration of IGF-I.

2. IGFBP-2. IGFBP-2 is expressed early in embryogenesis (296) and by embryonic d 10 is highly expressed in neuroectoderm structures including the neural tube and neuroepithelium (296). During development, the most prominent

sites of IGFBP-2 expression in the CNS comprise cells with nonneuronal phenotypes including the epithelium of the choroid plexus, the floor plate, and the infundibulum (30). Later in development, IGFBP-2 mRNA is detectable throughout the brain (33, 297), particularly in brain regions undergoing continuous remodelling as is the olfactory bulb (Fig. 1), the cerebellum, and the hippocampus (33, 35, 36, 297). IGFBP-2 expression correlates and complements that of IGF-II, and both IGFBP-2 and IGF-II protein are highly abundant in the cerebrospinal fluid (CSF) and choroid plexus (36). It is also known that IGFBP-2 binds IGF-II with a moderate preferential affinity over IGF-I (135).

IGFBP-2 associates to cell surface proteoglycans in rat brain tissue (134) and neuronal cells (136), and IGF-I/IGFBP-2/proteoglycan complexes have been identified in rat brain tissue (298), but the role of these cell membrane complexes is not completely understood. However, it has been suggested that differential localization of the IGFBPs in the pericellular and extracellular space, involving components of the extracellular matrix (111, 134–139), might regulate levels of diffusible/free IGFs. We have recently shown that IGF-I complexes with IGFBP-2 to promote neurogenesis in adult stem cells (213) and further demonstrated that neurogenesis was inhibited by IGFBP-2 antibody blockade (213), thus suggesting a key role for IGFBP-2 in this process. Additional evidence in support of an IGF-facilitating role for IGFBP-2 in the brain comes from colocalization of injected IGF-I with IGFBP-2 (299) and subsequent neuroprotection after hypoxic-ischemic injury, an effect not seen with an IGF variant that does not bind IGFBP-2 (300). It is therefore possible that brain IGFBP-2 regulates IGF-I cellular responses by facilitating receptor targeting of IGF-I or modulating IGF-I bioavailability in the pericellular space *in vivo* (111, 135). Cell-associated IGFBP-2 may therefore act as a "linker" molecule allowing pericellular storage of IGF.

This IGF-I storage might be affected by the presence of IGFBP-2 proteases (136, 281, 301, 302) that generate IGFBP-2 fragments which have markedly reduced binding affinity for the IGFs (135, 136). An IGFBP-2 fragment was identified on the cell surface of neuronal cells (136). The presence of this proteolytic fragment of IGFBP-2, capable of binding IGF-I while simultaneously being bound to the cell surface, might point to a process whereby proteolysis of membrane-bound IGFBP-2 provides a mechanism for creating peri-receptor low affinity IGF-I binding sites (136). Although we have recently demonstrated that IGFBP-2 proteolysis occurs during neuronal differentiation (281), the precise physiological significance of IGFBP-2 proteolysis in the nervous system remains to be determined.

Thus, IGFBP-2 possesses endocrine functions elicited by modulating serum IGF half-life and transport as well as autocrine/paracrine functions that result from blocking or enhancing the availability of IGFs to bind cell surface receptors. Despite these key functions, ablation of the *Igfbp-2* gene (303) generated a phenotype less dramatic than that initially predicted. Selective alterations were reported for spleen and liver size, whereas the level of other circulating IGFBPs was found to be increased in the adult animals (304). The absence of a "brain phenotype" in the *Igfbp-2* $-/-$ mouse (303) suggests functional redundancy in the IGFBP family during development of the CNS (305).

The IGFBP-2 transgenic mouse model developed by the Hoeflich group (306) has suggested that IGFBP-2 may be a negative regulator of postnatal growth, including brain growth, in rodents, potentially by reducing the bioavailability of IGF-I. These effects were seen even when hemizygous cytomegalovirus-IGFBP-2 transgenic mice were crossed with hemizygous phosphoenolpyruvate carboxykinase-bovine GH transgenic mice (with very high GH and IGF-I serum levels) (307), thus suggesting an inhibitory role for IGFBP-2 *in vivo*. However, in both studies (306, 307), IGFBP-2 was constitutively overexpressed in most tissues, including the brain, resulting in very high IGFBP-2 levels, and therefore it might be possible that any specific local enhancing activities of IGFBP-2 were overridden by the high systemic level of IGFBP-2. It is therefore possible that although IGFBP-2 is abundantly expressed in the brain, expression at nonphysiological levels (up to 9-fold over the normal endogenous levels) in the transgenic mice would dramatically change local brain IGF availability leading to the reported effects on brain size.

An example of physiological change in local brain levels of IGFBP-2 and how this might affect IGF action has been reported by Cardona-Gomez *et al.* (308) in a specialized group of glial cells of the third ventricle named tanycytes. These cells have the ability to accumulate IGF-I and thus regulate IGF-I availability (309–311). Cardona-Gomez's data show that estradiol and progesterone regulate local levels of IGFBP-2, including "peri-IGF-I-receptor" IGFBP-2 (308), and that these changes affect accumulation of IGF-I in tanycytes. This accumulation process might involve interaction of IGF-I with cell surface-associated IGFBP-2 before IGF-I being intracellularly translocated (308).

3. IGFBP-3. IGFBP-3 is normally expressed at a low level in the CNS, mainly in nonneuronal structures including epithelial cells (35, 37, 312, 313), and the effects of IGFBP-3 gene deletion on CNS are either unknown or have not been reported.

Nevertheless, in a study by Ajo *et al.* (201), IGFBP-3 was found to be up-regulated in rat cerebral cortical cells after GH stimulation. Ajo *et al.* show that GH promotes proliferation of neural precursors, neurogenesis, and gliogenesis and that these responses are mediated by locally produced IGF-I and its modulator IGFBP-3.

Conversely, a study by Rensink *et al.* (314), investigating the mechanisms of amyloid-β (Aβ) deposition in cerebral blood vessel walls and Abeta-induced toxicity in AD, proposed that IGFBP-3 might contribute to neuronal degeneration in AD. It is therefore possible that, as seen in other systems, IGFBP-3 might promote either enhancement or inhibition of IGF-I action in brain cells *in vitro*, depending on the experimental conditions.

The function of IGFBP-3 *in vivo* has been in part elucidated by the IGFBP-3 transgenic mouse model. This mouse showed modest intrauterine and postnatal growth retardation despite elevated circulating IGF-I levels (315). These mice showed a significant reduction in birth weight, reduction in litter size, and postnatal reduction of both body weight and

length and organ size. No change in brain growth or phenotype has been reported in IGFBP-3 transgenic mice (316).

4. IGFBP-4. IGFBP-4 is normally expressed at a very low level in the CNS, where its mRNA is found in a variety of brain cell types including meningeal cells, astrocytes, and fetal neuronal cells (317). During early brain development, IGFBP-4 expression is increased, and its mRNA is easily detectable in regions such as the choroid plexus, meninges, and the basal ganglia (318). Postnatally, IGFBP-4 mRNA is found in the meningeal cell layer surrounding the developing cerebellum in the hippocampal formation and olfactory bulb (Fig. 1) (35, 317). In some of these IGFBP-4-expressing brain regions, which maintain a degree of tissue remodelling/plasticity (38), local expression for IGF-I and its receptor is also seen, thus suggesting that IGFBP-4 may play a role as a local modulator of IGF action (318).

Overexpression of IGFBP-4 gene has only been recently investigated in smooth muscle cell-rich tissue, and therefore the effects to the nervous tissue are unknown.

As discussed earlier, IGFBP-4 generally acts *in vitro* and *in vivo* as a potent inhibitor of IGF-I action (147, 319–322), and it is therefore intriguing to find IGFBP-4 in sites where IGF-I exerts its primary mitogenic and trophic actions. A potential explanation might come from the work of Pintar *et al.* (305) on IGFBP-4 null mice, which indicates, contrary to expectation, that these mice have lower weight at birth. In this case, the authors argued that the absence of IGFBP-4 diminished tissue IGF storage capacity (305). This would imply that physiological levels of IGFBP-4 are indeed required for normal growth. Whether ablation of the IGFBP-4 gene also affects the CNS of these mice was not reported.

5. IGFBP-5 IGFBP-5 gene expression is highly abundant during brain development (32). The early expression of IGFBP-5 at embryonic d 10.5 indicates a key role of this IGFBP during embryogenesis (323). This hypothesis is further supported by a recent study from Pera *et al.* (150) which shows that IGFBP-5, as well as three IGFs expressed in early embryos, promoted anterior development by increasing the head region in *Xenopus* embryos. Thus, active IGF signals, including IGFBP-5, appear to be required for anterior neural induction in *Xenopus* (150). Whether IGFBP-5 has similar functions in early mammalian neural development is not known.

In rodents, IGFBP-5 appears to be coexpressed with IGF-I in principal neurons of sensory relay systems, cerebellar cortex, hippocampal formation, and many other neuron-rich regions (32, 324), including the olfactory bulb (Fig. 1) (35). These data point to the presence of potential autocrine and paracrine interactions between IGFBP-5 and IGF-I in specific brain regions where IGFBP-5 may act as a modulator or determinant of IGF action (325).

In addition to this spatiotemporal coexpression of IGFBP-5 and IGF-I, it is now becoming clear that IGF-I specifically regulates IGFBP-5. Using two IGF-I transgenic mice lines, Ye and D'Ercole (326) demonstrated that IGF-I up-regulates IGFBP-5 expression *in vivo*. This increase is specific for IGFBP-5 mRNA, because the level of expression of IGFBP-2 and IGFBP-4 mRNAs in these mice was found unchanged (326). The effects of IGFBP-5 gene ablation to the brain have not been reported.

6. IGFBP-6. IGFBP-6 is poorly expressed in the nervous system, and information regarding its mRNA expression distribution, in both the developing and adult nervous system, is limited.

IGFBP-6's unique property of preferential binding to the IGF-II ligand (327), coupled with the fact that this ligand is the most abundantly expressed IGF in the adult CNS, suggests that the IGFBP-6/IGF-II complex has a unique role in modulating IGF-II function in the adult brain (286).

During CNS embryogenesis, IGFBP-6 expression is tightly restricted to trigeminal ganglia and, relative to the rest of the embryo, this structure has the highest expression (286). The expression in the forebrain and cerebellum does not occur until after postnatal d 21 and then is primarily associated with GABAergic interneurons (286). The highest levels of expression in the adult animal are in the hindbrain, spinal cord, cranial ganglia, and dorsal root ganglia (286). These nuclei in the hindbrain and periphery that express IGFBP-6 are all associated with the coordination of sensorimotor function in the cerebellum, which indicates an important role for the IGFBP-6/IGF-II complex in the function and maintenance of these systems.

As introduced earlier, IGFBP-6 preferentially binds IGF-II and is regarded as a relatively specific inhibitor of IGF-II actions (327). IGFBP-6 is often expressed in nonproliferative cells, and its expression is associated with inhibition of growth of tumor cells *in vitro* (281, 327, 328) and *in vivo* (327). These findings are also supported by overexpression of IGFBP-6 *in vivo*, a model recently developed by the Babajko group (329) with strong expression of IGFBP-6 in glial fibrillary acidic protein-positive cells. Preliminary analysis of the IGFBP-6 transgenic mouse shows reduced cerebellum size and weight combined with altered differentiation of astrocytes (329). Abnormalities in the hypothalamus and pituitary were also reported (329). The effects on the brain of IGFBP-6 gene ablation remain unknown.

V. The IGF System and Neuroendocrine Cross-Talk in the Nervous System

A. IGF-I and fibroblast growth factor (FGF)-2

In vivo, growth factors such as IGF-I do not exist in isolation. Hence, the presence of other growth factors (Fig. 2) may further modulate the biological activity of IGFs and cellular responses. This modulation can be seen in the neurogenic activity of IGF, which in many cases requires the presence of basic FGF or FGF-2 to function (21, 330, 331).

Torres-Aleman and co-workers (332) showed that in primary cultures of hypothalamic cells, FGF-2 combined with IGF-I, significantly increased the number of neurite bearing cells, above that seen when either one of the two growth factors was added in isolation. Indeed, it appeared that the observed effect of these two growth factors was synergistic (332).

In a study by Drago and co-workers (330), it was shown that by blocking the endogenous stimulation of IGF-I with an antibody, the ability of FGF-2 to stimulate the proliferation of precursor cells isolated from the neuroepithelium of embryonic d 10 mice was abrogated. In later work by Frodin and

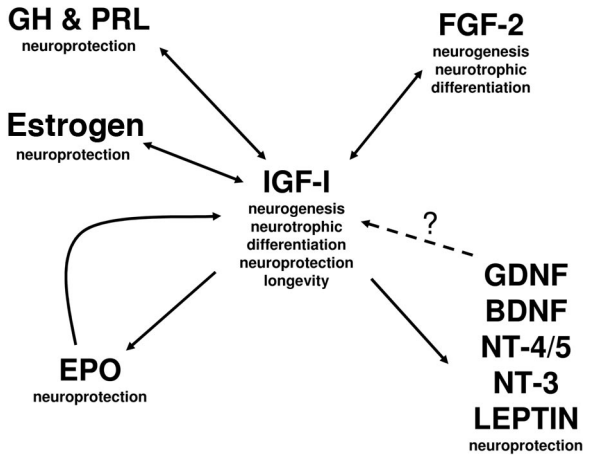

FIG. 2. Neuroendocrine cross-talk. *In vivo*, growth factors such as IGF-I do not exist in isolation. Hence, the presence of other growth factors may further modulate the biological activity and cellular responses of IGFs.

Gammeltoft (333), it was also found that the IGFs act synergistically with FGF-2 and nerve growth factor to promote chromaffin cell proliferation. A recent study from our laboratory (281) demonstrated, in neuroblastoma cells, that FGF-2 overrides IGF-I mitogenic and survival activity via induction of neuronal differentiation and blockade of the antiapoptotic response of IGF-I.

Furthermore, Torres-Aleman (243) recently highlighted the importance of a number of serum growth factors (in contrast to brain-produced), which included IGF-I, FGF-2, and other blood-borne neurotrophic factors (neurotrophins), in neuroprotective surveillance. All these factors exerted a tonic trophic input on brain cells, providing defense mechanisms ranging from blockade of neuronal death to up-regulation of neurogenesis.

B. IGF-I and neurotrophic factors

Increased interest has recently been devoted to the interaction of IGF-I with other "classic" neurotrophic factors. A study by Corse *et al.* (334) has investigated the potential effects of neuroprotective factors including IGF-I, glial cell line-derived neurotrophic factor, brain-derived neurotrophic factor, neurotrophin (NT)-4 and -3 (NT-4/5, NT-3), and ciliary neurotrophic factor on mature motor neurons. Only IGF-I, glial cell line-derived neurotrophic factor, and NT-4/5 were found to be potently neuroprotective, pointing to the potential combined use of these neuroprotective factors in treatment of neurodegenerative diseases. Subsequently, the results from a number of phase III clinical trials with nerve growth factor, brain-derived neurotrophic factor, and IGF-I (335) indicate that these neurotrophic factors may find an application in degenerative disorders or injury of peripheral nerves and motor neurons (336).

C. IGF-I and GH

Although GH gene expression also occurs in the central and peripheral nervous system, with brain GH imunoreactivity not affected by hypophysectomy (337) (178), the potential cross-talk between the IGF system and GH in the nervous system has not been fully investigated. Several experimental models, *in vivo* and *in vitro*, support a key role for GH in brain development. The Snell dwarf mouse (Pit1) and the GHRH receptor-deficient little mouse exhibit microcephalic cerebra with hypomyelination and retarded neuronal growth with poor synaptogenesis. Postnatal GH administration normalizes neuronal growth in these mice (338, 339). Recent *in vivo* studies by the Williams group have demonstrated that GH is involved in neuroprotection during hypoxic/ischemic brain injury (340–342). In these studies, they also showed GH-like immunoreactivity on injured brain cells and demonstrated that GH administered intracerebroventricularly is capable of preventing brain cell loss (340–342). Whether the neurogenicprotective effects of GH involve IGF-I induction is not clear.

However, some recent *in vitro* studies by Ajo *et al.* (337) have demonstrated that GH promotes proliferation and differentiation of fetal cerebral cortical cells in primary culture, and these effects are mediated by IGF-I. Furthermore, a study by Edmondson and co-workers (343) has demonstrated that GH and IGF-I promote growth and survival of melanocytes (neural-crest derived cells) by a process synergistic with FGF-2.

Furthermore, there is some evidence that the GH-related hormone prolactin (PRL) also possesses neurogenic properties. In female mice during pregnancy, PRL stimulates production of neuronal progenitors in the forebrain subventricular zone (344, 345). Whether the neurogenic properties of PRL are a direct effect of its action or mediated by other factors, including IGF-I, remains to be determined.

D. IGF-I and erythropoietin

Erythropoietin (EPO) is traditionally known as a hematopoietic cytokine produced by the fetal liver and adult kidney in response to hypoxia (346–350). However, the expression of EPO and EPO-receptors in the CNS and the up-regulation of EPO by hypoxic-ischemic insult (346–350) suggest that this cytokine is an important mediator of the brain's response to injury. In fact, *in vivo* EPO administration protects hippocampal CA1 neurons and retinal neurons from ischemic damage and prevents brain injury after a number of "insults" (346–350) by mechanisms involving both inhibition of apoptosis and neurotrophic actions (346–352). In the brain, EPO expression, regulated by the hypoxia-inducible factor (HIF)-1α, is mainly found in astrocytes.

Recent work by Wang *et al.* (353) demonstrated that IGF-I protection of primary neuronal cells exposed to low oxygen concentration correlates with activation of HIF-1α expression (351, 352). In the same studies using an *in vivo* model of hypoxia/ischemic brain injury, they also show that IGF-I transcriptional activation correlates with that of HIF-1α, suggesting that HIF-1α might mediate some of the IGF-I responses. In another study by Chavez and LaManna (354), it was shown that IGF-I induces HIF-1α transcriptional activity in rat cerebral cortex and neuronal cells (PC12) and that this induction is abolished by a selective IGF-I receptor antagonist (JB-1) (354). Furthermore, an early study by Feldser and

co-workers (355), in hepatoma cells, not only showed that insulin, IGF-I, and IGF-II induced HIF-1α expression but also demonstrated that HIF-1α is required for expression of IGF-II, IGFBP-2, and IGFBP-3 (355).

These findings suggest the presence of a potential complex synergistic cross-talk between the IGF and the EPO system involving both activation of common intracellular signaling pathways and regulation of gene expression. The presence of synergistic cross-talk between the IGF and the EPO system in neuronal cells has recently been demonstrated by Digicaylioglu and co-workers (356), showing that EPO can exert a more immediate neuroprotective action when administered in concert with IGF-I. The neuroprotective mechanism, after coadministration of EPO and IGF-I, involved synergistic activation of the PI3K–Akt pathway (356). These findings further support the concept that the coadministration of synergistic neuroprotective agents rather than a single agent might provide improved therapeutic outcome. Thus, treatment with appropiate combinations of EPO and IGF-I could be a future therapeutic strategy for a variety of acute neurological events (356).

E. IGF-I and sex steroids

Among the numerous endocrine systems regulating brain physiology, sex steroids play an important role. However, it appears that part of the effects of these hormones on the brain are mediated by trophic factors including IGF-I (357–361). Studies from the Garcia-Segura group (357–361) have demonstrated that estradiol and IGF-I increase survival and differentiation of developing fetal rat hypothalamic neurons. They have demonstrated that estrogen-induced activation of the estrogen receptor requires the presence of IGF-I and that both estradiol and IGF-I use the estrogen receptor to mediate their trophic effects on hypothalamic cells. *In vivo* sex steroids affect IGF-I levels in the endocrine hypothalamus, arcuate nucleus, and median eminence (357–361).

Furthermore, increased clinical and basic evidence suggests that gonadal steroids affect the onset and progression of several neurodegenerative diseases and schizophrenia and the recovery from traumatic neurological injury such as stroke. In the brain, similarly to the IGF system, both estrogen synthesis and estrogen receptor expression are up-regulated at sites of injury (362, 363). Once again, it is suggested that the neuroprotective effects of estrogen may be exerted independently of the classical nuclear estrogen receptors involving modulation of the IGF-I signaling (362, 363). This is supported by the fact that estrogen receptors and IGF-I receptor interact in the activation of PI3K and MAPK signaling cascades and possibly in the promotion of neuroprotection (362, 363). It is therefore possible that the decrease in estrogen and IGF-I levels with aging may thus result in an increased risk for neuronal pathological alterations. Also, in this case these findings suggest the presence of a potential complex synergistic cross-talk between the IGF and sex steroids involving activation of common intracellular signaling pathways, however the precise mechanism remains unclear.

VI. Altered Expression of the IGF System in Response to CNS Injury

A role for endogenous IGFs in the injured brain is suggested by a number of studies showing the induction of components of the IGF system after transient unilateral hypoxic/ischemic injury and stroke in the rat model (364–371) (Fig. 3, A–C). IGF-I mRNA induction is seen within infarcted regions by 3 d after hypoxia (369) (Fig. 3A). In addition, IGF-II (365), IGFBP-2 (365, 370) (Fig. 3C), IGFBP-3 (369) (Fig. 3A), and IGFBP-5 (368) (Fig. 3B) genes are differentially induced in specific regions after hypoxic/ischemic injury in the same model, suggesting that they may modulate the actions of IGF-I in a spatiotemporal-specific manner. The induced expression of IGF-I and IGFBP-2, -3, -4, and -5 in reactive microglia, oligodendrocytes, astrocytes, and surviving neurons (313, 370) of the periinfarcted area, including areas distant from the region of cell loss, suggests a role for the local IGFBPs in transporting IGF-I from its sites of production to the sites of action (313) (Fig. 3, A–C). Furthermore, in the periinfarcted regions, IGFBP-2 was highly expressed by reactive astrocytes that were juxtaposed to surviving neurons (Fig. 3C) (313), therefore suggesting a specific role for IGFBP-2 in augmenting IGF-I action (313) (Fig. 4).

A facilitative role of IGFBP-2 in IGF-I action in the nervous system is also suggested by a study from the Gluckman group (299). Using the hypoxic-ischemic brain injury rat model, we have demonstrated that centrally administrated (intracerebroventricular) ^{3}H-IGF-I is rapidly translocated to neurons and glia in injured sites (299) and that the tritiated IGF-I signal colocalized with IGFBP-2 protein in neurons and glia from the cerebral cortex and subregions of the hippocampus. The ^{3}H-IGF-I signal persisted for up to 6 h after administration, suggesting local storage of the IGF-I molecule (299). These data, together with their previous reports on the inefficacy of the IGF-I analog des(1-3) IGF-I to rescue hypoxic-ischemic injured neurons (300), further suggest that local IGFBPs (*i.e.*, IGFBP-2) play a key role in IGF-I delivery to the injured site (299, 313) (Fig. 4). These findings might point to a role for cell-associated IGFBP-2 (134) to modulate local IGF-I bioavailability (Fig. 4).

IGFBP-2 mRNA is induced throughout the injured hemisphere (313) (Fig. 3C) whereas IGFBP-3 is only moderately induced in reactive microglia and glial cells and is substantially decreased in neuronal cells of the region of injury (372) (Fig. 3A). However, in the early stages of the injury response, IGFBP-3 expression increases rapidly in vascular endothelial cells throughout the affected hemisphere with maximal expression levels at 24 h, which then become undetectable 48 h later (372). This early transient induction of IGFBP-3 in brain vascular endothelial cells is a likely mechanism by which brain vascular endothelial cells potentially regulate up-take of circulating IGFs after the hypoxic-ischemic insult (372). However, the precise mechanism involved remains to be determined. Nevertheless, these data might point to a potential role for IGFBP-3 as carrier/transporter of vascular IGF-I into the brain tissue in the early phases of the injury response, when local IGF-I availability and expression might not be sufficient to trigger the neuroprotective mechanisms (Fig. 4).

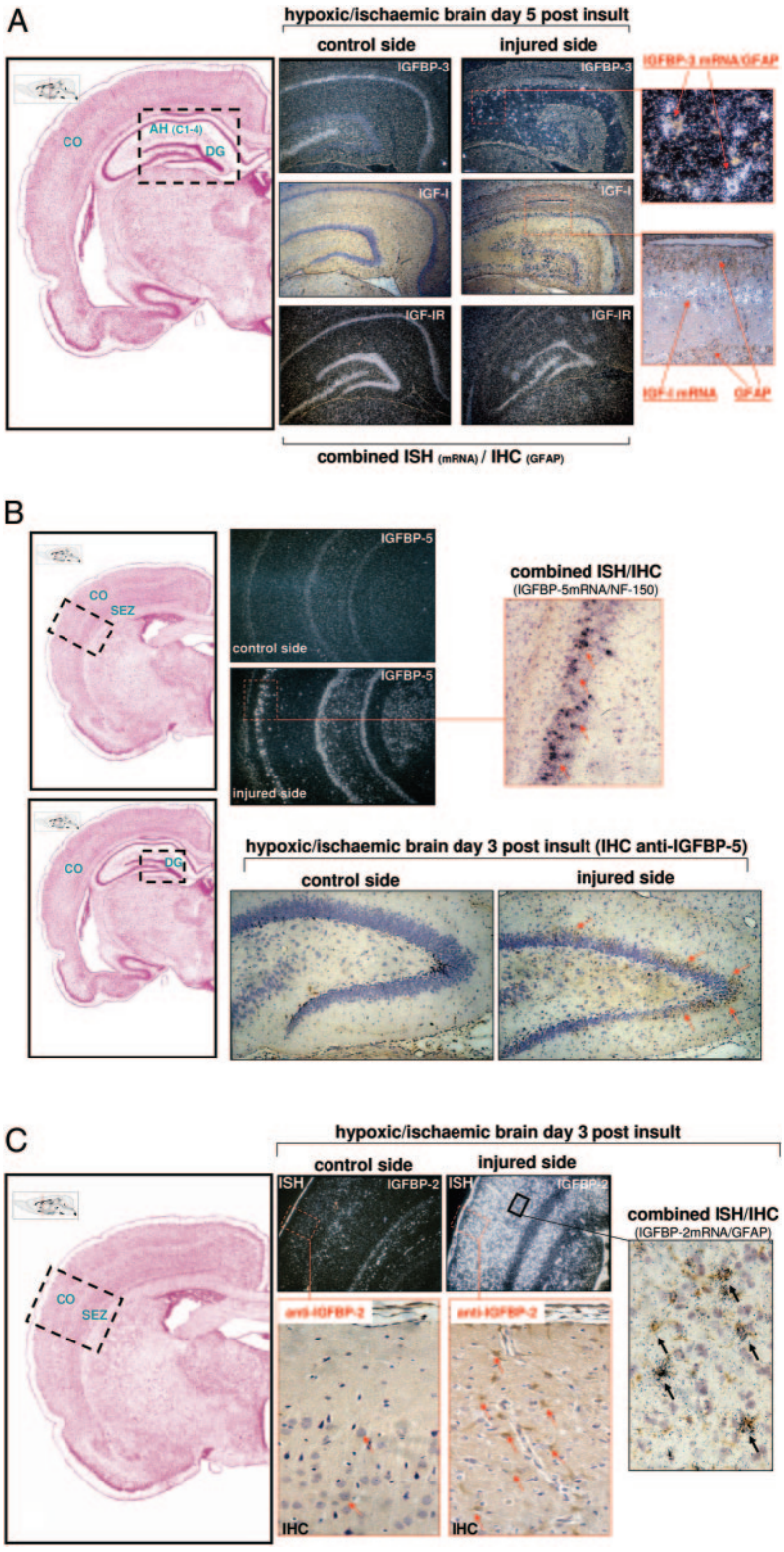

FIG. 3. Altered expression of the IGF system in response to CNS injury. A role for endogenous IGF system in the injured brain is suggested by a number of studies showing the induction of components of the IGF system after transient unilateral hypoxic/ischemic injury and stroke in the rat model. IGF-I mRNA induction is seen within infarcted regions by 3–5 d after hypoxia/ischemic brain injury (d 5 after insult is shown). In addition, IGF-I receptor and IGFBPs genes are differentially induced in specific regions after hypoxic/ischemic injury in the same model, suggesting that they may modulate the actions of IGF-I in a spatiotemporal-specific manner (d 3 and 5 after insult are shown). In panels A–C, IGF-I, IGF-I receptor, IGFBP-3, IGFBP-5, and IGFBP-2 mRNA were detected by *in situ* hybridization (ISH; 5-μm paraffin sections). Immunohistochemical staining for glial fibrillary acid protein (GFAP) is shown in panels A and C, whereas staining for the 150-kDa neurofilament (150 kDa-NF) is shown in panel B. Immunoreactivity for IGFBP-2 is shown in panel C. CO, Cortex; AH, Ammon's horn; DG, dentate gyrus; IHC, immunoistochemistry. Hematoxylin-eosin staining is shown in the *left panels* [obtained from L. W. Swanson: Brain Maps: Structures of the Rat Brain, 2nd edition, Elsevier, Amsterdam, 1998/1999 (528), with permission from Elsevier].

After hypoxic-ischemic insult, IGFBP-4 mRNA is also moderately up-regulated (365, 368). This is also true for IGFBP-5 (Fig. 3B), which is up-regulated after severe hypoxic-ischemic injury in the infant rat brain (368), and its mRNA is up-regulated in cerebellar granule cells during apoptosis (325). In both cases, the increase of IGFBP-5 expression is believed to be required to maximize the availability of IGF and thus potentiate the IGF-triggered survival signaling, as has previously been described for cerebellar granule cells (325).

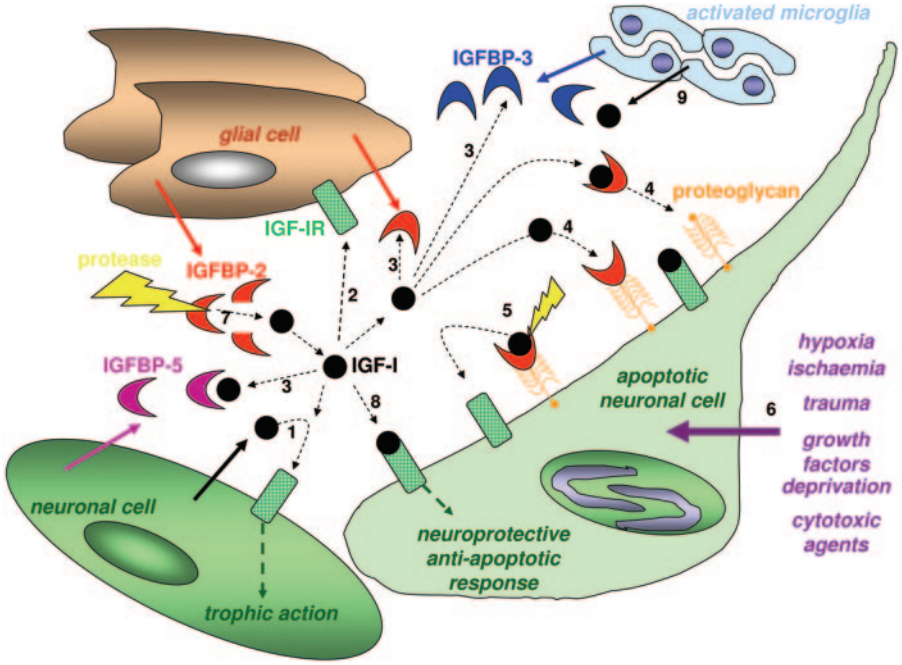

FIG. 4. A model for neurotrophic and neuroprotective actions of IGF-I in brain. Secreted IGF-I exerts local autocrine (1) or paracrine (2) trophic actions. A family of IGFBPs (3) modulates IGF-I bioavailability. IGFBP-2, the most abundant brain IGFBP, mediates pericellular storage of IGF-I via interaction with cell surface proteoglycans (PG) (4) or components of the extracellular matrix. Cell surface IGF-I/IGFBP-2/PG complexes (4) are suggested to play a role in targeting of IGF-I to its membrane receptors. IGFBP-2 mediated IGF-I receptor targeting at the cell surface, and this event might be further potentiated by the presence of a specific IGFBP-2 protease (5), which generates IGFBP-2 fragments that have reduced affinity for IGF-I. In response to a number of cerebral insults (*i.e.*, hypoxia/ischemic brain injury) (6), IGFBP-2 proteolysis might also affect the level of pericelluar IGF-I (7), therefore augmenting its neuroprotective activity (8). Following cerebral insult activation and recruitment of specialized brain cells (9) might further contribute to modulate the local IGF system (9).

After peripheral nerve injury (lumbar motoneurons), IGFBP-6 mRNA and its protein expression are strongly upregulated in the spinal motoneurons. This increased expression of IGFBP-6 in the damaged nerve is spatiotemporally associated with a local increased expression of the IGFs (373). It is therefore likely that IGFBP-6 might play a specific role in controlling IGF availability to lesioned motoneurons and thus regulates axonal regeneration (373). These findings all suggest that the IGFs in the brain, after injury, may act as endogenous neuroprotective agents and limit the degree of neuronal and glial loss (Fig. 4).

VII. Altered Expression of the IGF System in Malignancies of the Nervous System

IGF-IR plays a crucial role in the induction and maintenance of the malignant phenotype. Increased expression of IGF-I, IGF-II, and IGF-IR is present in a wide range of human cancers (374), including lung, breast, thyroid, and prostate carcinomas, rhabdomyosarcomas, leukemias, and the peripheral nervous system tumor neuroblastoma (375, 376). IGF-IR overexpression leads to cellular transformation (374, 377), tumor cell proliferation (378, 379), and growth (380), whereas disruption of IGF-IR expression reverses the transformed phenotype (374, 377).

Within the CNS, the IGF family is critical for normal development: aberrant expression and/or activation may be associated with CNS malignancy (381, 382). Components of the IGF system, in particular IGF-I, IGF-II, and the IGF-IR, are overexpressed to varying degrees in numerous CNS tumors (381, 383), including low-grade gliomas, glioblastomas, medulloblastomas, astrocytomas, ependymomas, and meningiomas.

Expression of the IGF family in CNS malignancy has been most thoroughly investigated in glioblastoma. IGF-IR expression is higher in glioblastomas than in normal brain, and glioblastoma cell lines exhibit a dose-dependent IGF-I stimulation of both receptor autophosphorylation and thymidine incorporation, indicating a functional receptor (384). Both ligands for the IGF-IR, IGF-I and IGF-II, have increased mRNA transcript formation in glioblastoma compared with normal brain, and the major IGF-II transcript of 6.0 kb found in glioblastoma is similar to that found in fetal brain (385). The IGF ligands are also secreted into the CSF of glioblastoma patients (386). Most of the IGF binding proteins, including IGFBP-1, -2, -3, -5, and -6, are expressed in glioblastomas, with the most abundant being IGFBP-3 (387). In addition, glioblastomas express membrane-bound forms of the binding proteins, and IGFBP-3 is secreted into culture media (387). Much of the *in vitro* work on the role of IGF-IR in transformation has been performed in rat glioblastoma cell lines. In this work, researchers have found through mutational analyses that distinct regions of IGF-IR are critical for the biological actions of the IGF ligands, including mitogenesis, transformation, and differentiation, through the induction of specific downstream targets (388–392).

IGF ligands acting through the IGF-IR are known to affect several aspects of glioblastoma tumor formation in addition to growth and transformation. IGF-I stimulates the migration (393) and invasion (394) of glioblastoma cell lines in culture, prerequisites for tumor cell metastasis. IGF-I acts as a potent survival factor in glioblastoma cell lines, even overcoming proapoptotic stimuli (394, 395). Glioblastoma cell treatment with IGF-I triple helix-forming DNA (396–398), antisense IGF-IR (399–402), kinase-defective IGF-IR (403), or additional IGF-IR mutant dominant-negative constructs (404) all induce growth suppression and/or apoptosis, resulting in decreased tumor growth. These studies have led the way for future work on IGF-IR inhibition and ligand interference in glioblastoma patient therapy (382).

As previously indicated, expression of IGF system components is also altered in other CNS tumors. In infiltrating astrocytomas, IGF-IR expression increases early in tumor

development, appearing in stage II tumors and continuing into stage IV (204). IGF-IR protein levels are increased in the majority of medulloblastoma cases, with concomitant increases in phosphorylated forms of the downstream signaling molecules Erk-1, Erk-2, and Akt/PKB (405, 406). When IGF-II or activated Akt/PKB is retrovirally transferred into neural progenitors along with sonic hedgehog-patched, medulloblastomas form (407), suggesting a role for this pathway in tumor formation. In microarray analyses of ependymomas, high IGF-II expression was detected (408). High IGF-II expression occurs in meningiomas, and the IGF-II/IGFBP-2 ratio, indicating free IGF-II levels, correlates with tumor anaplastic histopathology (381). In fact, meningiomas express the highest IGF-II mRNA levels of all intracranial tumors (409). Although IGF ligand levels are increased in the majority of CNS tumors, ligand increases are not detected in the CSF, indicating that IGFs act locally in an autocrine and paracrine fashion to control tumor cell proliferation (386). This idea is supported by studies in both primary intracranial tumors and brain metastases from non-small cell lung tumors that show that interference with the IGF-I/IGF-IR autocrine signaling prevents cell growth (410, 411).

The IGF system is also important in neuroblastomas, which typically occur peripherally but are occasionally found intracranially. IGF expression is present in all stages of primary neuroblastoma tumors (412). IGF-I or IGF-II coupled to IGF-IR promotes both autocrine and paracrine growth and survival of human neuroblastoma cell lines (413–418). IGF-IR overexpression protects neuroblastoma from apoptosis (75, 275, 378, 419–423), whereas inhibition of IGF-IR using antisense strategies blocks tumor growth and induces regression of neuroblastoma tumors in mice (424). Because neuroblastoma is also thought to arise through improper differentiation, these studies coupled with the CNS tumor reports suggest a critical role for the IGF family in nervous system tumor development and growth.

VIII. IGF-I Therapy in Nervous System Disease Models

A. IGF-I therapy in acute central nervous system disease

After hypoxic/ischemic brain injury in the 21-d-old rat, cell death in the pyramidal cells of the CA1/2 region, striatum, thalamus, and cortical layers 3–5 of the ligated hemisphere becomes evident within a few hours, is maximal by 24–72 h after injury, and then reduces (367). In contrast, the level of endogenous IGF-I mRNA does not rise until after 24 h from injury, becoming maximal by d 5 (235). This is compatible with earlier observations that after traumatic brain injury (425), bioassayable neurotrophic activity in cortical wounds is not induced until 6 d after injury in adult rats and 3 d after injury in infant rats. These observations of a temporal mismatch between the induction of cell death and the expression of neurotrophic activity led to the hypothesis that earlier administration of potential neurotrophins such as IGF-I might be neuroprotective.

In adult rats with unilateral hypoperfusion injury, intracerebroventricular administration of IGF-I 2 h after injury was shown to be neuroprotective in a dose-dependent fashion (369, 426) with a marked reduction in cortical infarction, suggesting that both neurons and glia are protected (426). The window of opportunity for neuronal rescue was limited to only within 2 h of injury, but could be extended by several hours if combined with postischemic hypothermia. The latter treatment is assumed to slow the processes of delayed cell death (299, 426). The effects of IGF-I were shown to enhance functional as well as histological outcome (427). The late apoptosis that continues for many days after a stroke-like injury is also inhibited by acute postischemic IGF (427). The neuroprotective action of IGF-I is likely to be dependent on the capacity of IGFBPs to translocate IGF-I from the CSF to the site of injury. IGF-II administered in conjunction with IGF-I attenuates the neuroprotective effect of IGF-I, possibly by competing for IGFBPs (300).

In rats, intranasal IGF-I reduced neuronal infarction after middle cerebral artery occlusion (428, 429). Other studies have confirmed the neuroprotective effect of IGF-I in spinal cord injury (430), and in the late gestation fetal sheep subject to cerebral ischemia (431). In addition, there is indirect evidence in rats of improved cognitive function after traumatic brain injury treated with IGF-I (432). Studies in the fetal sheep also suggest that IGF-I can protect oligodendrocytes and, thus, myelin production (433). This is compatible with the observation that in overexpressing IGF-I transgenic mice there is a reduced number of apoptotic oligodendrocytes (278). However, it has also been shown that IGF-I causes an increase in microglial number and increased gliosis, as indicated by the density of reactive astrocytes, and both of these cell types, in turn, express IGF-I (207, 433).

B. IGF-I therapy in chronic central nervous system disease

IGF-I has also been explored in chronic neurological disease. Clinical trials of IGF-I have been conducted in MN disease (434–437) based on preclinical *in vitro*, *in ovo*, and *in vivo* observations in a variety of rodent models (438–440). The results have been conflicting. A recent systematic review concluded that although IGF-I therapy may have a modest effect, the current data are insufficient for definitive conclusions (434). It is also difficult in such studies to separate effects on the CNS from peripheral effects, for example, on muscle.

Experimental autoimmune encephalomyelitis is used as a preclinical model for multiple sclerosis. In this model, IGF-I is reported to improve neurological and histological outcome (441, 442). More recently, it has been shown that if IGF-I is given before motor signs of encephalomyelitis are obvious, it appears to delay disease onset. Once disease takes hold, however, it shows either no beneficial effect on remyelination (443) or worsens disease outcome, particularly if the levels of bioavailable IGF-I are increased by coadministration with IGFBP-3 (444). Similarly, it has been suggested that chronic IGF-I administration may have some therapeutic role in AD (162, 445, 446). IGF-I *in vitro* inhibits amyloid induced neuronal death (266), induces choline acetyl-transferase (445), and affects CNS amyloid-β levels (162). Studies of this kind are limited by the poor transfer of IGF-I across the intact blood-brain barrier. However, IGF-I will cross the compromised blood-brain barrier, as in multiple sclerosis or other

acute syndromes (447), and new delivery approaches are in development (448).

C. IGF-I therapy in neurodegenerative disorders

1. MN disease. MN disease is a heterogeneous group of neurodegenerative disorders that selectively affect upper and/or lower MN leading to muscle atrophy and weakness. This disease of late middle age is relentlessly progressive and almost invariably lethal within 5 yr of onset of symptoms. Amytrophic lateral sclerosis (ALS) accounts for approximately 80% of all cases of MN disease and has an estimated incidence of three to five cases per 100,000 (449). Of the remaining patients, some will have a familial form of ALS, due to a mutation in cytosolic Cu/Zn superoxide dismutase (SOD1) (450). Although it is not known exactly how mutant SOD1 injures MN, mice overexpressing mutant SOD1 develop a denervating illness that resembles ALS despite normal or increased levels of wild-type SOD1 activity (449).

Accumulating data support the therapeutic use of IGF-I in the treatment of ALS. As discussed earlier, IGF-I is essential for normal development (37, 451) and is the only known neurotrophic factor capable of supporting both sensory and motor nerve regeneration in adult animals (37, 451). The ability of IGF-I to promote neuronal survival is directly related to its potent antiapoptotic properties (376). IGF-I prevents apoptosis in MN (439, 452), glial cells (reviewed in Ref. 376), and muscle cells (reviewed in Ref. 453), all cell types affected by ALS (454). IGF-I serum levels are decreased in ALS patients (455) and could contribute to the development of disease (455, 456). IGF-I preserves MNs in the *wobbler* mouse (457), and expression of the IGF-I receptor is increased in the spinal cord of ALS patients, suggesting that there may be a compensatory increase in IGF-I receptor (458). Two placebo-controlled trials of IGF-I in ALS patients have produced mixed results. The North American ALS/IGF-I Study Group found that patients receiving IGF-I daily for 9 months had slower disease progression and reported a better quality of life than placebo-treated controls (435). However, the European ALS/IGF-I Study Group showed no benefit to IGF-I therapy in a similar paradigm (437). Thus, although the sc administration of IGF-I to ALS patients was of uncertain clinical benefit (435, 459), the data were sufficiently promising to support another multicenter clinical trial. The Great Lakes ALS Consortium, under the direction of the Mayo Clinic, is currently entering patients into a new double-blind placebo control trial of sc IGF-I in the treatment of ALS (www.alsa.org). The clinical data in man also lead investigators to employ viral gene therapy for targeted delivery of IGF-I to MN in mouse models of ALS. Retrograde delivery of IGF-I to MN occurs after im injection of IGF-I linked to adeno-associated virus and prolongs survival in a mouse model of ALS (439). The Robert Packard ALS Center at Johns Hopkins is proposing a trial of adeno-associated virus-IGF-I in ALS patients to begin within 1 yr (www.alscenter.org).

2. AD. AD, the most common type of senile dementia in the elderly, is characterized neuropathologically by the presence of intracellular neurofibrillary tangles, extracellular diffuse neuritic plaques, and the loss of neurons in a defined region of the brain (460–464). The neuritic plaque contains amyloid filaments, dystrophic neurites, activated microglia, and astrocytes. The principal component of amyloid fibrils is the β-amyloid peptide (Aβ) (460, 462, 465). Although accumulation of amyloid plaques in the brain (463, 464) appears to be the major cause of familial AD onset, the role of this neuroanatomical alteration in sporadic forms of the disease is not fully understood. Evidence suggests that altered levels of growth factors and/or their receptors, which exert trophic and survival function in the nervous system, may underly neuronal degeneration as seen in AD brain (466–468). Metabolic and hormonal functions decline in a variety of severe age-associated pathologies, including those associated with alterations in the insulin and IGF systems (162, 164, 445, 467, 469–472). AD patients show changes in circulating levels of both insulin and IGF-I, often associated with abnormal responses to insulin (473–475). Compelling evidence indicates that insulin and IGF-I have a direct effect on the metabolism and clearance of the Aβ (162, 446, 463, 476, 477). In neuronal cells, insulin inhibits Aβ degradation (162, 476, 477), directly increases Aβ secretion, and decreases the intracellular level of Aβ peptides by stimulating their intracellular trafficking (476, 477). On the other hand, serum IGF-I levels correlate with cerebral levels of Aβ in aged rodents (162, 446). Liver-specific deletion of the *igf-1* gene also has prematurely increased cerebral levels of Aβ (162). IGF-I administration to aged rats decreases the level of Aβ in the brain parenchyma to the levels found in young rats (162, 446), which is balanced by increased levels of Aβ in the CSF (162, 446). IGF-I increases Aβ clearance from the brain by enhancing transport of Aβ-carrier proteins into the brain through the choroid plexus (162). The effects of IGF-I on Aβ clearance are ablated by TNFα, a cytokine involved in neurodegeneration-associated brain impairment (162, 446, 477).

Decreased circulating insulin and IGF-I might influence the development of neurofibrillary tangles, another AD "marker." This process appears to be a consequence of altered tau phosphorylation, a major component of neurofibrillary tangles (477–479). Nonphosphorylated tau protein plays a key role in the assembly of tubulin monomers into microtubules to constitute the neuronal microtubule network, which is necessary to maintain neuronal cell shape and axonal transport (477–479). However, hyperphosphorylation of tau, as seen in AD, produces destabilization and dissociation of microtubules, forming abnormal filaments that aggregate in neurofibrillary tangles (477–479). Insulin and IGF-I reduce tau phosphorylation and promote tau binding to microtubules in neuronal cells (480–483), whereas disruption of insulin and IGF-I signaling, as seen in the IRS-2 knockout mouse model (483), increases tau phosphorylation as seen in AD. These findings indicate a potential key role for insulin and IGF-I in regulating tau protein phosphorylation, a failure of which augments the onset of neurofibrillary-tangle AD pathology. The role of other IGF system components, such as the IGFBPs, in AD pathology remains unclear (474, 484).

The data discussed above point to insulin and IGF-I signaling as a potential therapeutic target in AD. The effects of IGF-I on key AD markers (*i.e.*, amyloid toxicity, tau phosphorylation) suggest the potential usefulness of this growth

factor in the treatment of neurodegenerative diseases. The primary challenge in translating successful use of IGF-I in laboratory research models to growth factor therapy in the clinic is delivery of IGF-I to the brain in sufficient concentrations to influence neuronal functions (445, 448, 477). A number of recent novel approaches might offer solutions to this problem. Born *et al.* (485), and more recently De Rosa's group (486), have illustrated growth factor delivery to the brain via intranasal administration. Carrascosa *et al.* (448) have succesfully used IGF-I microsphere therapy (sc delivery) in rodents to prevent Purkinje cell degeneration. These studies suggest that IGF-I may potentially be delivered to the brain to prevent pathophysiological changes associated with the development of AD.

D. Neuropathy: a potential target for IGF-I therapy

The study of the IGF system in peripheral nerve injury has focused on both crush and transection of the sciatic nerve. Sciatic nerve crush in the rat increases IGF-I mRNA distal to the crush site, whereas IGF-I expression at the crush site is not increased until 4 d after injury (487). IGF-I and IGF-IR up-regulation are observed after sciatic nerve transection (373, 488). During the first 3–7 d after transection, the expressed IGF-I is localized mainly in Schwann cells of the intact nerve and the distal stump (488, 489). IGF-I expression has also been detected in transected facial nerve 4–7 d after transection, where it is mainly localized in astrocyte processes (490).

IGF-I supports neurite outgrowth in guinea pig myenteric plexus neurons, (491) chick sympathetic and motor neurons (272, 492, 493), and rat sensory and sympathetic neurons (265, 494). Most of the evidence for IGF-promoted neurite extension comes from studies of transected peripheral nerves. For example, rats treated with IGF-I after sciatic nerve transection exhibit increased MN survival and re-innervation of muscle, showing that IGF-I mediates functional neurite regeneration *in vivo* (495). Functional sciatic nerve regeneration is also promoted by IGF-I treatment in mice after sciatic nerve crush (496). The spatiotemporal regulation patterns of the IGFs and IGF-IR suggest a functional endogenous role of the IGF system in neurite regeneration after injury.

Because of these neurite-promoting effects, IGFs may have a role in the treatment of neuropathy, particularly in the treatment of diabetic neuropathy. Decreased IGF expression may contribute to the development of diabetic neuropathy (497–499); sc IGF-II restores pain and pressure thresholds toward normal in diabetic rodents (497), whereas IGF-I and IGF-II increase sciatic nerve regeneration after injury in rodents with diabetes (500). The beneficial effects of IGF are not limited to peripheral neuropathy, with reported therapeutic effects of IGF-I in a rat model of diabetic autonomic neuropathy (501). Studies have also shown that IGFs may have a therapeutic role in chemotherapy-induced neuropathies. IGF-I can prevent vincristine-, cisplatinum-, and taxol-mediated neuropathies (502, 503).

E. Targeting the IGF/IGF-IR signaling in cancer therapy

Interference with IGF ligand and IGF-IR autocrine or paracrine signaling provides a novel therapeutic target for CNS malignancies (504). In fact, targeting IGF-IR expression and signaling is a new therapeutic approach to cancer treatment in numerous tumor types (380, 505, 506). A truncated IGF-IR that acts as a dominant negative receptor or antisense RNA to IGF-IR prevents metastatic breast carcinoma (399, 507). A kinase-defective IGF-IR dominant negative receptor and α-IR3, the IGF-IR blocking antibody, inhibit glioblastoma tumor growth in mice, as discussed above (403). A dominant negative IGF-IR introduced using retroviral infection decreases pancreatic tumor burden, particularly when used in combination with chemotherapeutic drugs (508). Antisense IGF-IR strategies also enhance the susceptibility of Ewing's sarcoma to doxorubicin-induced apoptosis (509), implying a use for IGF-IR disruption in combinatorial drug therapy (388). Other cancers for which IGF-IR interference is effective as a treatment strategy include melanoma, lung carcinoma, ovarian carcinoma, and rhabdomyosarcoma (reviewed in Ref. 510). One problem with these treatment strategies in the CNS is delivery, although direct injection into brain tumors or implantation of antisense IGF-IR-containing cells via craniotomy (400) has proven effective. However, gene therapy approaches will likely be more advantageous and less traumatic for IGF-I inhibition treatment paradigms in CNS tumors (511). Additional human clinical trials targeting both the IGF-IR and IGF-I are ongoing (381, 382).

F. The potential therapeutic use of N-terminal peptides derived from IGF-I

The hypothesis that IGF-I might be degraded by removal of an N-terminal peptide to leave des-N-(1-3) IGF-I, which would have lower affinity for the IGFBPs but maintain affinity for the receptor, was first suggested by Sara and colleagues (512). However, des-IGF-I has subsequently been shown to be markedly less neuroprotective than IGF-I (300). This suggested the possibility that the N-terminal tripeptide, GPE, might itself have biological function. Sara *et al.* (512) previously showed that GPE stimulates dopamine and acetylcholine release, and Bourguignon and Gerard (513) have presented data suggesting that GPE might act as a NMDA receptor antagonist, followed by a report that GPE can prevent NMDA-induced neuronal toxicity *in vitro* (512).

The effect of GPE in models of brain disease has since been extensively investigated. GPE given centrally or as an iv infusion has marked neuroprotective effects in rodent models of hypoxic-ischemic injury (514). The window of opportunity is considerably longer than for IGF-I and extends for greater than 11 h after injury (514). GPE protects a wide variety of neuronal phenotypes and after hypoxic-ischemic injury prevents the loss of choline acetyltransferase-expressing neurons and up-regulates neuronal nitric oxide synthase (514). It has also been demonstrated to be protective in neurotoxic models of brain disease induced by 6-hydroxydopamine (515) and by quinolinic acid (516). The actions of GPE include neuronal protection and inhibition of both caspase-3-dependent and caspase-3-independent neuronal cell death and protection of astrocytes. The tripeptide is now in phase 1 clinical studies for use as an acute neuroprotectant.

IX. Perspectives for Future Directions

Since the discovery of Salmon and Daughaday (1) in 1957, a considerable body of investigation has been devoted to defining the role of the IGF system in many tissues, including the brain. There is no doubt that these pleiotropic factors, in concert with their receptor and binding proteins, are involved in controlling key processes in brain development and traumatic or degenerative disorders of the nervous system.

Although the development of *in vivo* models such as the transgenic and knockout mice or disease/injury models has contributed to providing unique information about the growth promoting, neurogenic and neuroprotective actions of the IGF system, much research remains. An area of study that is currently receiving more interest from a large number of investigators is that related to stem cell research in the developing and adult brain. It is well known that progenitor cells in the dentate gyrus of hippocampus and the subventricular zone of lateral ventricles generate new neurons throughout the life of mammals, however very little is known about how stem and progenitor cells "decide" whether to proliferate or exit the cell cycle. Some of these events are directly or indirectly controlled by the IGFs, and therefore detailed studies directed to understand the mechanisms by which the IGFs control neuronal proliferation and differentiation and the complex intracellular signaling cross-talk activated by these ligands are required. Knowledge in this area could be of potential relevance to neurodegenerative disorders such as AD.

Intriguingly, and in contrast to the mentioned role of IGF-I in normal physiology, recent data on the role of IGF and insulin signaling pathways on longevity in *Caenorhabditis elegans*, *Drosophila*, and rodents suggest that partial blockade of these signaling systems dramatically extends life span (517–524). In *C. elegans*, restoration of IGF signaling in neuronal cells, but not other cell systems, reverses the extended longevity, suggesting that IGF signaling in the nervous system is critical in this process (517, 518, 525). Reduced nutrition, which lowers circulating and brain IGF content is similarly effective in enhancing longevity (518), whereas in *C. elegans* selective ablation of nutritionally responsive olfactory and gustatory neurons (IGF receptor-rich regions in mammals) similarly extends longevity (526, 527).

The mechanisms by which IGF and nutritional responsive regions of the brain regulate longevity remain unclear, but paradoxically too much IGF in the brain may enhance neuronal survival but may reduce the life span of the organism.

Although there is an increasing body of evidence for the potent antiapoptotic and neuroprotective effects of IGF-I, we still lack a clear understanding of the *in vivo* cellular and molecular mechanisms involved. This is a critical goal to be achieved for the development of IGF-I based preventive protective and regenerative therapies. However, it should be remembered that *in vivo*, IGF-I does not act in isolation and other growth factors might potentially modulate its biological action (Fig. 2). It is critical therefore to develop improved *in vitro* and *in vivo* models for the investigation of these potential interactions and the mechanisms involved.

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Fifth International Symposium on Hormonal Carcinogenesis
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The Hormonal Carcinogenesis Symposia is a forum to foster scientific collaborations and the exchange of the latest developments to advance our knowledge of hormonal cancers (e.g., breast, prostate, ovarian, endometrial). The goal of this Symposium is to focus on significant advances in the rapidly growing field of hormonal cancers by bringing together world leading scientists working at the cutting edge of endocrine-related cancer research. With this new information arising from this meeting, it will foster progress for improved strategies for the prevention and treatment of these malignancies, so prevalent in the USA and worldwide. The 1st International Symposium on Hormonal Carcinogenesis was in 1991 in Cancun, Mexico; the 2nd in 1994 at the Karolinska Institute, Stockholm, Sweden; the 3rd in 1998 at the Fred Hutchinson Cancer Center, Seattle, Washington; and the 4th in 2003 at the Instituto Valenciano de Oncologia in Valencia, Spain. All four symposia received overwhelmingly excellent ratings by participants.