

The Insulin-Like Growth Factor System and Neurological Complications in Diabetes

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The IGF system plays vital roles in neuronal development, metabolism, regeneration and survival. It consists of IGF-I, IGF-II, insulin, IGF-I-receptor, and those of IGF-II and insulin as well as IGF-binding proteins. In the last decades it has become clear that perturbations of the IGF system play important roles in the pathogenesis of diabetic neurological complications. In the peripheral nervous system IGF-I, insulin, and C-peptide particularly in type 1 diabetes participate in the development of axonal degenerative changes and contributes to impaired regenerative capacities. These abnormalities of the IGF system appear to be less pronounced in type 2 diabetes, which may in part account for the relatively milder neurological complications in this type of diabetes. The members of the IGF system also provide anti-apoptotic effects on both peripheral and central nervous system neurons. Furthermore, both insulin and C-peptide and probably IGF-I possess gene regulatory capacities on myelin constituents and axonal cytoskeletal proteins. Therefore, replenishment of various members of the IGF system provides a reasonable rationale for prevention and treatment of diabetic neurological complications.

Keywords C-Peptide; Diabetic Encephalopathy; Diabetic Neuropathy; IGF's; Insulin

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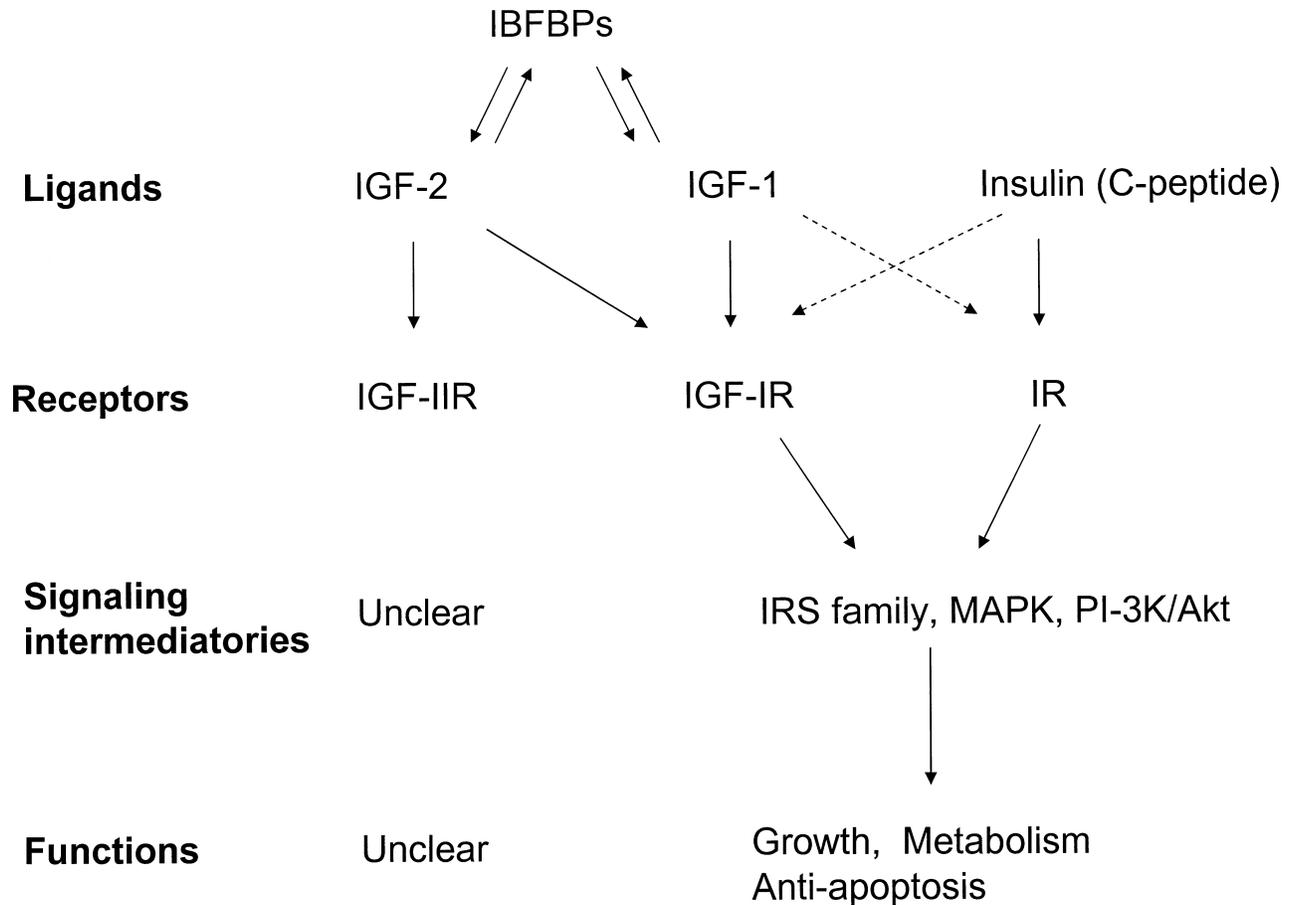
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INTRODUCTION

Definition of the Insulin-Like Growth Factor (IGF) System

The IGF system consists of IGF-I, IGF-II, insulin, insulin-like growth factor receptors (IGF-IRs), insulin receptor (IR), and IGF-binding proteins (IGFBPs) (Le Roith, 1999). IGF-I and IGF-II are single-chain polypeptides similar to that of proinsulin and their amino acid sequences share extensive homologies with insulin (Blundell et al., 1983; Rinderknecht and Humbel, 1978). Both IGF-I and IGF-II signal predominantly via the IGF-IR, whereas insulin acts primarily through the IR. IGF-IR and IR are tyrosine kinase receptors characterized by $\alpha_2\beta_2$ heterotetramers that are held by disulfide bonds (Ullrich and Schlessinger, 1990). The β subunit of IGF-IR shares a high homology (84%) with that of IR, whereas the cysteine-rich pockets of the α subunit of IGF-IR shows low homology (48%) with that of IR (Ullrich et al., 1986). IGF-I and insulin bind weakly to each other's receptors, with a 1000-fold lower affinity than that for the cognate receptor (Kjeldsen et al., 1991). IGF-IIR is a receptor that differs from IGF-IR and IR, as it has a single transmembrane protein bearing binding sites for mannose-6-phosphate-containing residues (Kieiss et al., 1994), while IGF-IR and IR are tyrosine kinase receptors (Figure 1).

In spite of their structural similarities, IGF-IR and IR mediate different effects: mainly metabolic effects for IR and predominantly growth effects for IGF-IR. The mechanisms underlying the specificities of the IGF-IR and IR signaling are not totally clear. Several mechanisms are probably of importance, such as differences in tissue distribution, modulation of ligand binding by local environments, such as IGFBPs, and differences in

**FIGURE 1**

Summary of IGF system. The IGF system consists of IGF-I, IGF-II, insulin, insulin-like growth factor receptors (IGF-IR and IGF-IIR), insulin receptor (IR), and IGF-binding proteins (IGFBPs). In addition to these are the insulinomimetic C-peptide. IGF-I and IGF-II are single-chain polypeptides and bind to IGF-IR with high affinity, whereas insulin acts primarily through the IR. IGF-IIR is a single transmembrane peptide bearing binding sites for mannose-6-phosphate, its signaling and function being unclear. IGF-I and IGF-II are interactive with IGFBPs, whereas insulin does not bind to IGFBPs. Although IGF-IR and IR utilize similar signaling pathways, IGF-IR and IR mediate different effects: mainly metabolic effects for IR and predominantly growth effects for IGF-IR. In addition, recent studies have shown that both IGF-IR and IR mediate antiapoptotic effects. The weak binding of IGF-I/IGF-II to IR and insulin to IGF-IR are indicated with dotted lines. C-peptide shows insulin-like effects, although its receptor binding is not clear. It appears to regulate the expression of both IGF-I, IGF-II, IGF-IR, and IR possibly, via NF- κ B.

downstream substrates (Blakesley et al., 1996). To define functional specificity, mutations of the various domains of IGF-IR and IR have been performed. For IGF-IR, the tyrosine cluster 1131, 1135, and 1136 (Gronborg et al., 1993; Li et al., 1994) and tyrosine 950 (Miura et al., 1995a) are crucial for both mitogenic and transformation activities, but not for antiapoptotic activity. Substitution of tyrosine 1251 with phenylalanine results in a loss of the antiapoptotic activity (O'Connor et al., 1997) and a reduced transformation activity, but it does not affect mitogenicity (Miura et al., 1995b). These data indicate that domains required for inhibition of apoptosis are distinct from those essential for both transformation and mitogenicity. With

respect to the IR, mutation experiments have established relationships between phosphorylation of specific receptor sites and activation of the receptor kinase activity (Avruch et al., 1990; Flores-Riveros et al., 1989; Tavaré and Denton, 1988; Tornqvist et al., 1987; White et al., 1988). The Tyr-1150 domain, including three tyrosine residues at positions 1146, 1150, and 1151, is crucial for IR tyrosine kinase activity (Hashimoto et al., 1992). Mutation at the ATP binding sites (Lys-1018 or Lys-1030 in the β subunit of IR) leads to loss of insulin-stimulated kinase activity (Chou et al., 1987; Ebina et al., 1987). In contrast, the phosphorylation of tyrosines 1316 and 1322 in the carboxyl-terminal region do not influence the receptor kinase activity (Maegawa

et al., 1988; Myers et al., 1991; Takata et al., 1991). These results suggest that specifically located tyrosine domains of the IR and IGF-IR may be required for specific ligand-induced cellular functions.

The IGFs are associated with high-molecular-weight carrier proteins, IGFFBPs, present in the circulation and brain (Baxter, 2000). Currently, six different IGFFBPs have been identified. They share a cysteine-rich region but differ substantially in other regions (Baxter, 1994; Katz et al., 1995). The interaction of IGFs with their receptor is controlled by IGFFBPs. Most of the IGFs in the circulation are bound to IGFFBPs, because the affinity of IGFs for the IGFFBPs is greater than that for the IGF receptors. When the affinity of IGFFBPs for IGFs is reduced, the IGFs are released to interact with the IGF receptors (Blakesley et al., 1996). Therefore, IGFFBPs act as partitioning agents controlling the amount of IGF that is available for receptor association. Three factors have been found to be important for regulation of IGFBP affinity: (a) association with extracellular matrix proteins reduces IGFBP affinity (Jones et al., 1993); (b) proteolytic cleavage of IGFBP reduces greatly the affinity for IGFs (Clemmons et al., 1998); and (c) phosphorylation of serine residues on IGFBP-1 results in 6- to 7-fold enhancement of its affinity for IGF-I (Jones et al., 1991). In the rat, IGFBP-3 is the principal carrier protein for IGFs in the circulation (Katz et al., 1995). Under physiological conditions, IGFBP-2, -3, -4, -5, and -6 are expressed in the central nervous system (CNS), IGFBP-2 being the predominant IGFBP (Walter et al., 1999). Diabetes affects the levels of IGFFBPs. IGFBP-1 is increased in streptozotocin (STZ)-induced diabetic rats and patients (De La Puente et al., 2000; Landau et al., 1995; Luo and Murphy, 1991; Park et al., 1998; Price et al., 1997; Rodgers et al., 1995), whereas IGFBP-3 is decreased (Cinaz et al., 1996; Graubert et al., 1991). The expression of IGFBP genes is regulated by insulin: insulin inhibits IGFBP-1 and stimulates IGFBP-3 gene transcription (Graubert et al., 1991; Katz et al., 1998).

In summary, the IGF system is a complicated system consisting of ligands, receptors, and interacting binding proteins. The components of this system interact with each other in a complicated mode. The ligands of the IGF system may interact with other receptors besides their own, for example, IGF-I binds to the IR and insulin binds to IGF-IR, however, with low affinities. Therefore, IGF-I signaling is not an isolated phenomenon. It is modulated by the presence of IGFFBPs, and probably by insulin and maybe by C-peptide. These interactive relationships account for the intricate function of the IGF system. As mentioned earlier, the IGF system consists of IGF-I, IGF-II, IGF-IR, IGF-IIR, IGFFBPs, and IR. To this series of associated trophic factors, we propose to add the proinsulin C-peptide as an interactive member of the system for reasons that will become clear.

Function of the IGF System

The IGF system plays a vital role in mediating growth, development, metabolism, and survival of many tissues and organs. In neuronal tissues, the IGF system supports the survival of neurons (Ang et al., 1992; Zackenfels et al., 1995; Zackenfels and Rohrer, 1993; Zheng et al., 2002) and Schwann cells (Cheng and Feldman, 1997; Syroid et al., 1999), regulates neuronal differentiation (Arsenijevic and Weiss, 1998; Brooker et al., 2000; Feldman et al., 1997; Morrione et al., 2000; Ochoa et al., 1997), enhances regeneration in cultured adult rat sensory neurons (Ferynhough et al., 1993), stimulates neurite outgrowth (Kim et al., 1997; Rind and von Bartheld, 2002; Wang et al., 1992; Zhang et al., 2001), enhances oligodendrocyte development (D'Ercole et al., 1996; Dubois-Dalq and Murray, 2000; Jiang et al., 2001; McMorris and McKinnon, 1996), promotes myelination of the nervous system (Cheng et al., 1999; Copelman et al., 2000; Hetts et al., 1997; Mozell and McMorris, 1991; Russell et al., 2000; Ye et al., 1995; Zackenfels et al., 1995), rescues neuronal loss following cerebral hypoxic-ischemic injury (Gluckman et al., 1992; Guan et al., 1993; Williams et al., 1995), and protects against neuronal apoptosis (Zawada et al., 1998; Zhang et al., 2002). IGF-I has been used in the treatment of several disorders, including growth deficiency, osteoporosis, catabolic disorders, diabetes, and neurodegenerative disorders (Dore et al., 1997). The rather unique propensity of IGF-I to act on a variety of neuronal cells might provide a general means of reducing or slowing down neuronal losses that occur following various brain insults.

IGF-I regulates calcium ion channel currents and neuronal excitability (Blair and Marshall, 1997; Hall et al., 1995; Ristic et al., 1998; Selinfreund and Blair, 1994). The rapid action of IGF-I on the voltage sensitivity of L-type calcium channel indicates that IGF-I, in addition to function as a mitogen with long-term effects, also acts as a rapid neuromodulator (Bence-Hanulec et al., 2000). IGF-I rapidly promotes phosphorylation of the $\alpha 1$ subunit of the calcium L-channel (Bence-Hanulec et al., 2000) and activates the phosphatidylinositol (PI) 3-kinase/Akt pathway (Blair et al., 1999), which may promote the survival of cerebellar granule neurons. Besides calcium channels, IGF-I up-regulates potassium channels through PI 3-kinase, PDK1, and SGK1 pathways to exert the proliferative action of the growth factor (Gamper et al., 2002) and it may modulate sodium channel expression (Craner et al., 2002).

Recent studies show that the IGF system plays antiapoptotic effects in various types of cells, including hematopoietic cells (Kelley et al., 1998; Zumkeller, 2002), osteoblasts (Hill et al., 1997; Kawakami et al., 1998; Tumber et al., 2000), fibroblasts (Buckley et al., 2002; Valentinis et al., 1999), melanoma cells (Kanter-Lewensohn et al., 2000), myoblasts (Foulstone et al., 2001; Hong et al., 2001), mouse embryonic fibroblast NIH3T3

cells (Sell et al., 1995), NWTb3 cells, NIH3T3 cells expressing the normal human IGF-IR (Heron-Milhavet et al., 2001), and epithelial cells (Moorehead et al., 2001; Wilkins et al., 2002). In neuronal cells, it promotes neuronal survival following ultraviolet (UV) irradiation (Kulik et al., 1997) and serum deprivation in PC12 cells (Parrizas et al., 1997b). It inhibits apoptosis of cerebellar granule neurons induced by low potassium (D'Mello et al., 1997; Galli et al., 1995), and protects against apoptosis of dorsal root ganglia (DRG) and Schwann cells exposed to high glucose (Delaney et al., 2001; Russell et al., 1999; Vincent et al., 2002) and neuroblastoma SH-SY5Y cells exposed to high concentration of mannitol or glucose (Cheng and Feldman, 1998; Matthews and Feldman, 1996; Singleton et al., 1996; van Golen and Feldman, 2000; Vestling et al., 2001; Vincent et al., 2002; Zhang et al., 2001) or to 3-morpholinopyridone (SIN-1), a peroxynitrite donor (Saeki et al., 2002). On the other hand, decreased IGF-I gene expression is found in Purkinje cells undergoing apoptosis (Zhang et al., 1997) and inhibition of IGF-I activity appears to contribute to premature apoptosis of cerebellar granule neurons in the weaver mutant mice (Zhong et al., 2002). IGF-I and IGF-II (3 to 100 ng/mL) each prevents glucose deprivation-induced neuronal damage in a dose-dependent manner in rat hippocampal and septal neuronal cell cultures, whereas insulin exhibits a protective effect at high concentrations (greater than 1 μ g/mL) and epithelial growth factor (EGF) does not show any protective effect at all (Cheng and Mattson, 1992). This latter study is in accordance with the results of other investigators, who show that the IGF-I, but not EGF and fibroblast growth factor (FGF), protects against c-Myc-induced apoptosis in Rat-1 fibroblasts via the activation of IGF-IR (Harrington et al., 1994), and that the IGF-I, but not acidic FGF (aFGF), basic FGF (bFGF), nerve growth factor (NGF), and platelet-derived growth factor (PDGF), rescues neuroblastoma SH-SY5Y apoptosis induced by hyperosmolarity (van Golen and Feldman, 2000). Therefore, it is well documented that IGF-I exerts antiapoptotic effects via IGF-IR signaling.

The IGF-IR signaling may utilize multiple pathways in a cell type-specific manner to exert its antiapoptotic activity: the PI 3-kinase/Akt pathway in Rat-1 cells, promyeloid cells, PC 12 cells, and DRG neurons (Dudek et al., 1997; Liu et al., 1997; Parrizas et al., 1997b); the MAP (mitogen-activated protein) kinase pathway in PC 12 cells (Cano et al., 1996); the Crk-II-enhanced Ras-dependent but Raf-1/MAP kinase-independent pathway in human embryonic kidney 293 cells (Parrizas et al., 1997a); the stress-activated p38 MAP kinase and c-Jun N-terminal kinase (JNK) pathway in neuroblastoma cells (Cheng and Feldman, 1998; Okubo et al., 1998; Zhang et al., 2001); p38 MAP kinase pathway in NWTb3 cells (Heron-Milhavet et al., 2001); up-regulation of Bcl-xl and activation of PI 3-kinase in Baf-3 cells (Leverrier et al., 1999); and

PI 3-kinase in mouse neocortical neuronal cell cultures (Ryu et al., 1999). Among the multiple signaling pathways that are involved in the IGF-IR-mediated antiapoptotic effect, PI 3-kinase/Akt pathway plays a key role and MAP kinase pathways are implicated. As illustrated in Figure 2a, binding of IGF-I/IGF-II to IGF-IR activates autophosphorylation of the receptor and phosphorylation of several intracellular substrate proteins (IRS family and Shc), and leads to activation of PI 3-kinase/Akt pathway and MAP kinase pathway (Figure 2). The activated Akt inactivates proapoptosis factors, such as Bad, p53, and caspase-3 (Bai et al., 1999; Brunet et al., 1999; Kermer et al., 2000; Yamaguchi et al., 2001); increases antiapoptosis factors, such as Bcl2 and Bclx (Leverrier et al., 1999; Li et al., 2001; Zhang et al., 2002); activates transcriptional factors, such as nuclear factor [NF]- κ B (Heck et al., 1999; Li et al., 2001) and cyclic AMP response element-binding protein (CREB) (Pugazhenthhi et al., 1999). It decreases forkhead transcription factor (FKH) (Brownawell et al., 2001; Kops and Burgering, 2000), which reduces expression of FKH target genes, including Fas ligand, and therefore decreases Fas-mediated apoptosis (Vincent and Feldman, 2002). With respect to the MAP kinase pathway, the activated extracellular signal-regulated kinase (ERK) inactivates Bad (Bonni et al., 1999; Scheid et al., 1999) and the p38 MAP kinase activates CREB (Bonni et al., 1999; Pugazhenthhi et al., 1999). Overall activation of these pathways results in antiapoptotic effects.

In contrast to IGF-IR, the IR-mitigated antiapoptotic effects are not totally clear. As shown in Figure 2b, insulin inhibits serum withdrawal induced Chinese hamster ovarian (CHO) cell apoptosis via a PI 3-kinase-dependent pathway (Lee-Kwon et al., 1998) and a Raf-1-dependent pathway, which leads to activation of NF- κ B (Bertrand et al., 1998) and the NF- κ B-dependent survival genes encoding tumor necrosis factor receptor-associated factor 2 (TRAF2) and manganese superoxide dismutase (Mn-SOD) (Bertrand et al., 1999). Insulin rescues serum-deprived immortalized brown adipocytes from apoptosis through PI 3-kinase/Akt pathways (Navarro et al., 2000), prevents cardiomyocytes from oxidative stress-induced apoptosis through activation of PI 3-kinase/Akt (Aikawa et al., 2000), and inhibits apoptosis of macrophage THP-1 cells, via a PI 3-kinase-dependent pathway (Iida et al., 2002). Data from our laboratory show that insulin activates p38 kinase, inhibits JNK, and promotes nuclear translocation of NF- κ B in neuroblastoma SH-SY5Y cells, indicating that these pathways are involved in IR-mediated antiapoptotic effects (Zhang et al., 2002).

Furthermore, recent studies show that other components of the IGF system besides IGF-IR, including IR and IGF-BPs, play antiapoptotic roles. Insulin exerts an antiapoptotic effect in various cell types, including external granular layer neurons in rat cerebellar slice cultures (Tanaka et al., 1995), Rat-1 fibroblasts

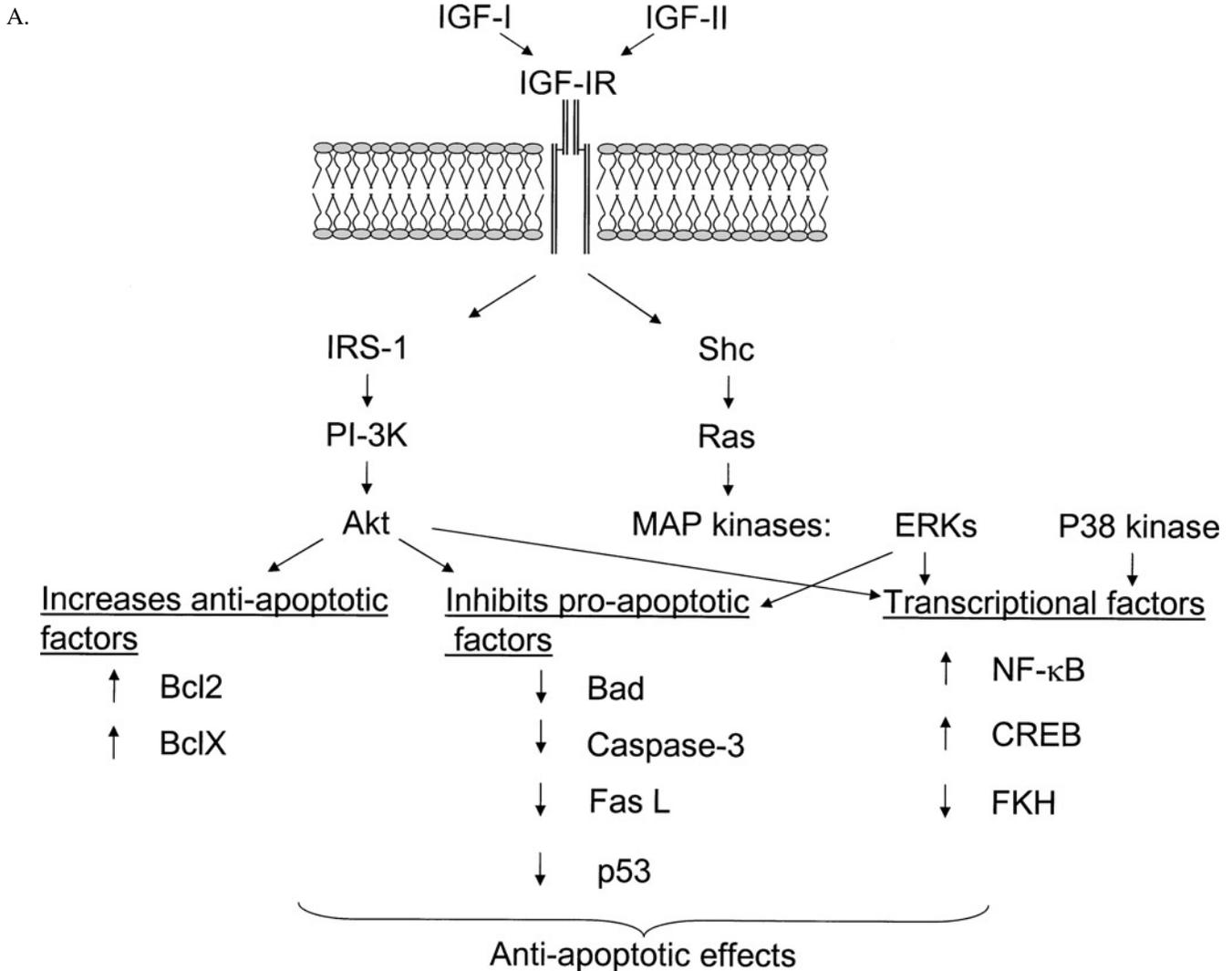


FIGURE 2

Summary of IGF-IR and IR pathways mediating antiapoptotic effects by IGFs. (A) IGF-IR signaling pathways. Binding of IGF-I/IGF-II to IGF-IR activates autophosphorylation of the receptor and of several intracellular substrate proteins (IRS family and Shc), leading to activation of PI 3-kinase/Akt pathway and MAP kinase pathway. The activated Akt inactivates proapoptosis factors, such as Bad, p53, and caspase-3; increases antiapoptosis factors, such as Bcl2 and Bclx; and activates transcriptional factors, such as nuclear factor (NF)- κ B and cyclic AMP response element binding protein (CREB). It decreases forkhead transcription factor (FKH), which reduces expression of FKH target genes, including Fas ligand and therefore decreases Fas-mediated apoptosis. With respect to the MAP kinase pathway, the activated extracellular signal-regulated kinase (ERK) inactivates Bad. The p38 MAP kinase activates CREB. Overall activation of these pathways results in antiapoptotic effects. (B) IR pathways. The IR-mitigated antiapoptotic effects are not totally clear. Insulin inhibits apoptosis via a PI 3-kinase/Akt pathway and a Raf-1-dependent pathway, each of which leads to activation of NF- κ B. The NF- κ B-dependent survival genes encoding tumor necrosis factor receptor-associated factor 2 (TRAF2) and manganese superoxide dismutase (Mn-SOD). Data from our laboratory show that insulin activates p38 kinase, inhibits JNK, and promotes nuclear translocation of NF- κ B in neuroblastoma SH-SY5Y cells (Zhang et al., 2002). All these pathways are involved in IR-mediated antiapoptotic effects.

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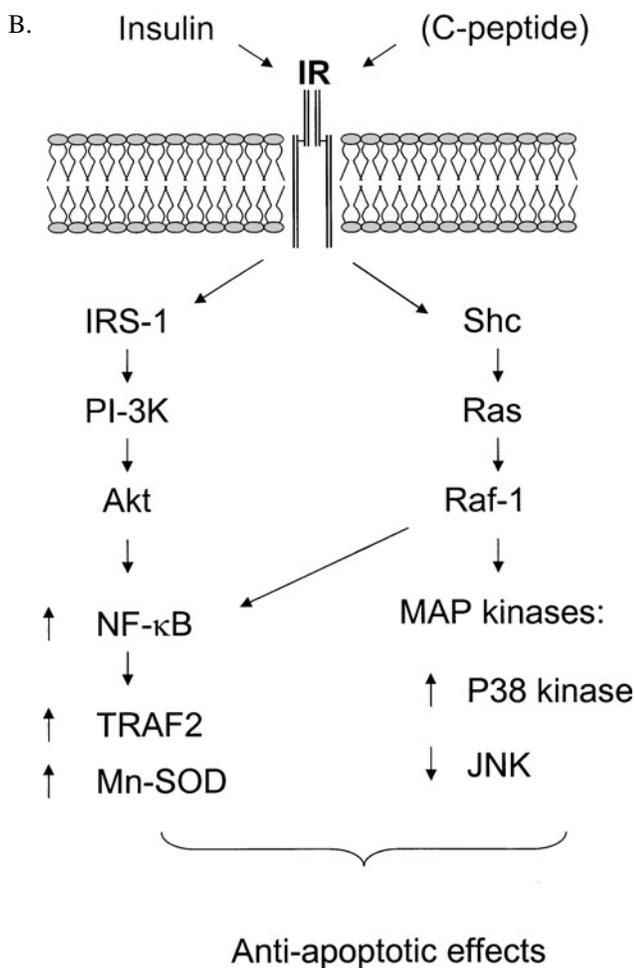


FIGURE 2
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(Kummer et al., 1997), macrophages (Iida et al., 2002), serum-deprived immortalized brown adipocytes (Navarro et al., 2000), cardiomyocytes of neonatal rats (Aikawa et al., 2000), and cultured rat adipocytes (Qian et al., 2001). In many studies, this effect was observed at high concentrations of insulin. It was therefore believed that the observed antiapoptotic function was mediated via IGF-IR and not by IR itself. However, Lee-Kwong et al. (1998), Bertrand et al. (1998), and Kummer et al. (1997) independently reported that low doses of insulin rescue CHO cells CHO or Rat-1 fibroblasts from apoptosis induced by serum starvation. These results indicate that IR indeed mediates an antiapoptotic effect. We have shown that low doses of insulin stimulate neurite outgrowth, enhance cell proliferation, and protect against high glucose-induced apoptosis of neuroblastoma SH-SY5Y cells (Zhang et al., 2001, 2002). These data support the notion that insulin plays an antiapoptotic function via its own receptors. Furthermore, the combination of low doses of

C-peptide and insulin give rise to an additive effect on neurite outgrowth, cell proliferation, and antiapoptosis in SH-SY5Y cells (Zhang et al., 2001, 2002), indicating that the proinsulin C-peptide may play an active role in the interactions of the IGF system.

IGFs are implicated in neurodegenerative disorders. Serum levels of insulin and IGFs and their binding proteins are perturbed in various human neurodegenerative disorders, such as Alzheimer's disease, amyotrophic lateral sclerosis, cerebellar ataxia, ataxia-telangiectasia (AT), and Charcot-Marie-Tooth 1A (CMT-1A) disease (Busiguina et al., 2000). Similarly, serum insulin and IGF-I levels are decreased in diabetic patients (Bereket et al., 1996; Cinaz et al., 1996; Clauson et al., 1998; Fujihara et al., 1996; Normann et al., 1994; Rieu and Binoux, 1985; Tan and Baxter, 1986). Furthermore, neuronal apoptosis has been demonstrated in both neurodegenerative disorders (Mattson, 2000; Mizuno et al., 1998; Tatton et al., 1997) and in experimental type 1 diabetes (Li et al., 2002a). These results suggest that similar mechanisms may be operable in a variety of neurodegenerative disorder and CNS complications of diabetes. However, more work is required to elucidate the potential pathogenic roles of IGFs in neurodegenerative disorders, such as Alzheimer's disease and the CNS complication of diabetes.

IGFBPs also play a role in the regulation of apoptosis. IGFBP-5 decreases apoptosis in human breast cancer cells (Perks et al., 2000), whereas IGFBP-3 increases apoptosis in the same cells (Baxter, 2001; Perks et al., 2000). Another antiapoptotic factor that may be related to the IGF system is the IGF-I-cleaving protease. It releases from the amino-terminal of IGF-I molecule a tripeptide Gly-Pro-Glu (Guan et al., 1999), which protects neuronal death in Huntington's disease, Parkinson's disease, cerebral hypoxic-ischemic injury, and *N*-methyl-D-aspartate (NMDA) toxicity (Alexi et al., 1999; Guan et al., 2000; Sara et al., 1989; Sizonenko et al., 2001).

NEUROLOGICAL COMPLICATIONS OF DIABETES

Diabetes is a chronic metabolic disorder that is reaching pandemic proportions. The two major forms are type 1 (or insulin-dependent) and type 2 (non-insulin-dependent) diabetes mellitus. They both have in common hyperglycemia and are apt to develop chronic complications such as nephropathy, neuropathy, retinopathy, and encephalopathy and to predispose to cardiovascular disease. Although both types of diabetes do develop chronic complications, they differ in their expression and progression, which is likely a reflection of differences in underlying pathogenetic mechanisms. For a long time, it was believed, and unfortunately still is to some extent, that hyperglycemia was the only culprit underlying the chronic complications of diabetes and hence by definition they were the same in the two types of

diabetes. In recent years, however, it has become increasingly evident that factors such as insulin deficiency and associated C-peptide deficiency, as well as progressive perturbations of trophic factors in type 1 diabetes play important roles in the pathophysiology in most of the chronic complications and may be responsible for the usually more severe forms of complications in this type of diabetes (Kohner, 1987; Marshall and Alberti, 1989; Mogensen, 1998; Sima et al., 1988; Sugimoto et al., 2000a).

The IGF system has been implicated in the pathogenesis of the chronic complications, such as the role of IGF-I in the development of diabetic neuropathy (Ishii, 1995), cardiovascular disease in type 2 diabetes (Janssen and Lamberts, 2002), and in diabetic angiopathy (Chiarelli et al., 2000; Janssen and Lamberts, 2000). In this article, we will focus on the neurological complications and IGFs, their neurotrophic effects that support nerve integrity and regeneration, and their protective effects on neuronal survival (Zhuang et al., 1997).

PERIPHERAL NEUROPATHY

Diabetic neuropathies as a group are the most common chronic complication of diabetes mellitus (Greene et al., 1997), but remain probably the least understood complication. The prevalence of diabetic neuropathy varies from 10% within 1 year of diagnosis of diabetes to 50% in patients with diabetes for more than 25 years (Dyck et al., 1993; Pirart, 1977; Sima, 1997; Vinik et al., 1992). Diabetic neuropathies include several distinct syndromes, among which distal symmetric polyneuropathy, often associated with diabetic autonomic neuropathy, is the most common and is referred to as diabetic polyneuropathy (DPN). The different syndromes affecting peripheral nerve can be separated into rapidly reversible manifestations and chronic progressive syndromes. The latter can be divided into symmetric polyneuropathies and focal/multifocal neuropathies (Sima, 1997; Sima et al., 1997c; Thomas, 1997).

The mechanisms underlying DPN are multiple and appear to involve several interrelated metabolic abnormalities consequent to hyperglycemia and insulin and C-peptide deficiencies (Greene et al., 1992, 1997; Sima, 1996; Sima and Sugimoto, 1999; Sima et al., 2001b; Sugimoto et al., 2000a, 2000c).

The results from the Diabetes Control and Complications Trial (DCCT) support this notion. Intensive glycemic control for 5 years reduced the incidence of clinical neuropathy by 60% in type 1 patients (The DCCT Research Group, 1993). The fact that strict hyperglycemic control did not completely prevent diabetic neuropathy (or any of the other complications), suggests additional pathogenetic attributes such as genetic predispositions, insulin/C-peptide deficiencies, and perturbations of trophic factors.

DPN shows a more severe clinical course in type 1 patients, associated with more severe structural changes compared to duration-matched type 2 patients (Dyck et al., 1999; Sima et al., 1988). Perturbations in the expression of insulin receptor and that of other growth factors and their receptors, either does not occur or are mild in a type 2 animal model (Pierson et al., 2002a). We and others (Sima et al., 2000, 2001a; Yagihashi, 1995; Yagihashi et al., 1994) have explored some of the differences in DPN in type 1 versus type 2 animal models. Comparisons of two isohyperglycemic models have demonstrated functional, biochemical, molecular, and structural differences, which have been ascribed to the presence/absence of insulin and/or the insulinomimetic C-peptide (Sima et al., 2000, 2001b). Type 1 DPN is in both experimental models and patients characterized by severe axonal atrophy resulting in a dying-back-type axonopathy with progressive nerve fiber loss. This latter phenomenon is probably in part due to impaired nerve fiber regeneration. Furthermore, progressive nodal and paranodal changes occur in type 1 but not in type 2 DPN. Type 2 DPN, on the other hand, shows a milder axonal atrophy, mild axonal loss, and normal regenerative capacity, but an increased frequency of segmental demyelination (Sima et al., 1986, 1988, 1997c; Sima and Sugimoto, 1999; Sugimoto et al., 2000a; Yagihashi, 1995; Yagihashi et al., 1994). It was recently shown that insulin treatment enhances the expression of IGF-I in sural nerves of diabetic patients (Grandis et al., 2001) and that C-peptide corrects partially the decreased activity of IGFs in hippocampus of type 1 diabetes (Li et al., 2002b), supporting the above notion.

IGFs and DPN

Unlike NGF, IGFs exert their neurotrophic effects on most peripheral nerve fibers, be they sensory, motor, or autonomic. The neurotrophic support by the IGF system was recognized in the mid 1980s (Ishii et al., 1985; Recio-Pinto and Ishii, 1984) when the effects of IGF-I and IGF-II on neurite outgrowth and cell survival were described. Similar effects by insulin and C-peptide were only described recently (Li et al., 2001, 2002b; Pierson et al., 2002a, 2002b, 2003). Like peripheral nerve expression of NGF, the deficit in IGF-I expression occurs gradually and is established at 6-week duration in the type 1 diabetic BB/Wor-rat (Pierson et al., 2002a; Tomlinson and Fernyhough, 2000; Xu and Sima, 2001).

Clinical Studies

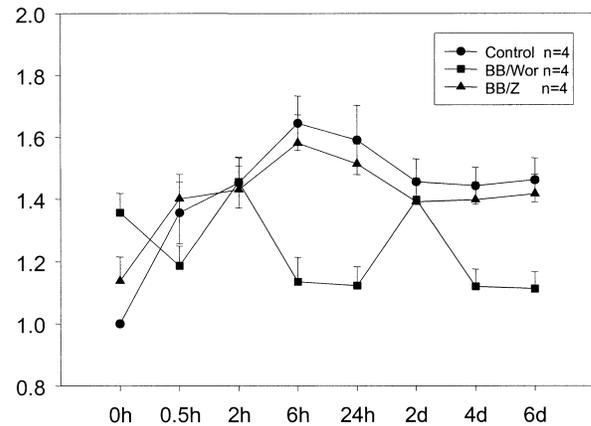
Circulating IGF-I activity is markedly reduced in both type 1 and type 2 diabetes (Arner et al., 1989; Ekman et al., 2000) and does not appear to correlate with the degree of glycemic control (Ekman et al., 2000). Crosby et al. (1992) showed decreased IGF-I and elevated IGFBP-I levels in type 1 patients

with peripheral neuropathy. In type 2 patients, those with clinical DPN showed significantly lower levels of IGF-I compared to diabetic patients without DPN or nondiabetic control subjects (Guo et al., 1999). Similar results were reported by Migdalis et al. (1995), who demonstrated decreased IGF-I plasma levels as well as decreased densities of IGF-IR on red blood cells in type 2 patients with sensory and autonomic neuropathy, compared to non-neuropathic patients and nondiabetic control subject. These findings suggest an association between DPN and impaired IGF-I activity. Of the other IGFs, insulin and C-peptide are certainly deficient in type 1 diabetes, whereas they may be increased systemically, at least in early insulin resistant type 2 diabetes. As to whether the peripheral insulin resistance of type 2 diabetes also applies to the peripheral and/or central nervous system is not known. These differences in the availability of IGFs, including insulin and C-peptide, are likely to account for some of the neurotrophic deprivations seen in type 1 diabetes and may relate to the generally more severe manifestations of DPN in type 1 diabetes (Sima and Sugimoto, 1999; Sugimoto et al., 2000a).

Experimental Studies

Neurotrophic factor activities in peripheral nerve tissues have been studied in both type 1 and type 2 diabetic animal models. In both the STZ and BB/Wor rats, there is a progressive reduction in NGF mRNA and other neurotrophins with duration of diabetes (Ferynhough et al., 1994, 1998; Pierson et al., 2002a, 2002b; Riaz and Tomlinson, 1996; Tomlinson and Ferynhough, 2000; Xu and Sima, 2001). Circulating levels of serum IGF-I are diminished (Bornfeldt et al., 1989; Sima et al., 1997b). In contrast, in type 2 animal models such as the ZDF(fa/fa) rat and the BB/Z rat (Sima et al., 1997a), IGF-I expression is not reduced in peripheral nerve or spinal cord (Pierson et al., 2002a, 2002b, 2003; Wuarin et al., 1994, 1996; Zhuang et al., 1997), whereas IGF-II gene expression is reduced in peripheral nerve of the ZDF(fa/fa) rat. Likewise, the expression of IGF-I and its receptor is significantly down-regulated in DRG and the superior cervical ganglion in type 1 animal models (Bitar et al., 1997; Craner et al., 2002; Ishii and Lupien, 1995; Pierson et al., 2003; Wuarin et al., 1994; Xu et al., 2002), but not in the type 2 BB/Z rat (Pierson et al., 2003). Because IGFs regulate the gene expression of neuroskeletal proteins such as tubulin and neurofilaments, which in turn are determinants for axonal caliber, these discrepancies between their expression in type 1 and type 2 animal models may account for the substantially milder axonal atrophy seen in the latter (Murakawa et al., 2002; Sima et al., 2000; Yagihashi et al., 1994) (Figure 3). This notion is supported by experiments demonstrating that infusion of either IGF-I or IGF-II into crushed sciatic nerves increases the distance of motor and sensory axon degeneration (Glazner et al.,

A. IGF-1R protein (DRG)



B. β -tubulin protein (DRG)

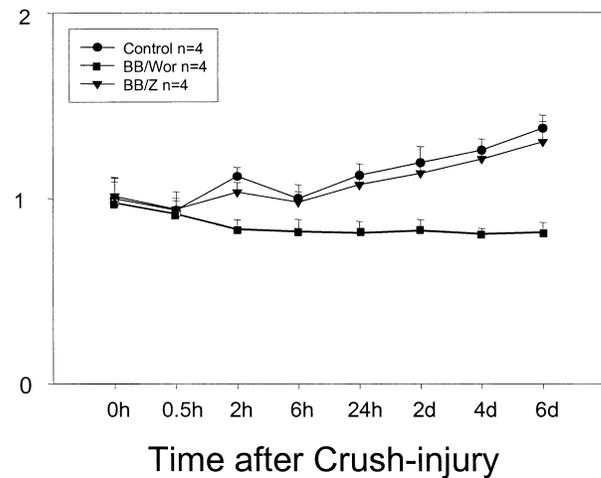


FIGURE 3

Protein expression of IGF-IR in dorsal root ganglia from type 1 diabetic BB/Wor and type 2 diabetic BB/Z rats at various time points after sciatic nerve crush injury (A). At baseline time point 0 in uninjured 6-week diabetic rats, the IGF-IR expression was significantly ($P < .001$) up-regulated in type 1 rats but not in type 2. Following crush-injury, type 2 diabetic rats showed an immediate upregulation of IGF-IR not significantly different from that of age-matched control animals, whereas the expression in type 1 rats showed an undulating and suppressed profile. Two-way ANOVA showed $P < .001$ ($F = 303$) for time and $P < .001$ ($F = 60$) for Group \times Time. This corresponded to a markedly suppressed expression of β -tubulin in type 1 diabetic rats (B), which from 24 hours post crush injury was significantly ($P < .001$) lower than in both control and type 2 BB/Z rats. Instead, isohyperglycemic and normoinsulinemic type 2 rats showed a normal up-regulation of β -tubulin. Reproduced with permission from *Journal of Neuropathology and Experimental Neurology*.

1993; Kanje et al., 1989). However, other ligands of the IGF family, such as insulin itself, as well as C-peptide, may in part account for these differences in the expression of neuroskeletal proteins. Insulin has neurotrophic effects on peripheral nerve by stabilizing neurofilament and tubulin gene expression in a dose-dependent manner (Fernyhough et al., 1993; Wang et al., 1992), and is required for NGF to exert its protective effects on human neuroblastoma cells (Recio-Pinto and Ishii, 1984). Similar effects have been demonstrated for C-peptide (Li et al., 2001; Pierson et al., 2003; Sima et al., 2002), and are probably mediated via C-peptide's insulinomimetic effects (Grunberger et al., 2001).

A preserved integrity of the IGF system is a requirement for normal nerve regeneration (Chiarelli et al., 2000; Ishii, 1995; Pu et al., 1999; Stoll and Muller, 1999; Xu and Sima, 2001). Nerve fiber regeneration is a spatiotemporally regulated multi-step process and a complex interplay between Schwann cells, macrophages, fibroblasts, and neuronal elements (Xu and Sima, 2001). Nerve damage induces early gene responses, which include the first wave of neurotrophic factors by Schwann cells, followed by macrophage recruitment and Wallerian degeneration, interleukin induction, Schwann cell proliferation, and the second wave of neurotrophic factor production (Xu and Sima, 2001). This cascade of interdependent events foster the synthesis of neuronal cytoskeletal elements that initiate and sustain axonal regrowth and regenerations. The early gene responses of trophic factors include the sequential up-regulation of IGF-I, c-fos, and NGF. In type 1 insulinopenic BB/Wor rat, this sequence of events is markedly delayed and suppressed in its magnitude (Pierson et al., 2002b; Xu and Sima, 2001), following sciatic nerve crush injury (Figure 3). These abnormalities are subsequently associated with perturbed expression of neurofilaments and tubulins and impaired fiber regeneration. Interestingly in the normoinsulinemic but isohyperglycemic type 2 BB/Z rat, these abnormalities do not occur or are substantially milder (Pierson et al., 2002b) and are prevented in the type 1 model following C-peptide replacement (Pierson et al., 2003), followed by normalization of neuroskeletal protein expression (Figure 4). These findings suggest that the perturbed regeneration in type 1 diabetes is not likely to be the result of hyperglycemia per se, but rather the consequence of insulin and/or C-peptide deficiency. This construct is also reflected by a close to normal nerve regeneration in the type 2 model and in C-peptide-replaced type 1 rats, the latter most likely mediated by C-peptide's insulin-enhancing effect (Grunberger et al., 2001).

Further effects of C-peptide replacement include normalization of the expression of IGF-I, IGF-IR, and the IR in peripheral nerve of type 1 BB/Wor rat (Sima et al., 2001a), which may be mediated via its effect on NF- κ B (Zhang et al., 2002).

One of the most profound differences between DPN in both human and experimental type 1 and type 2 DPN is the progressive nodal and paranodal changes occurring in the former (Sima et al., 1988; Sugimoto et al., 2000a). These changes consist of disruption of the paranodal barrier (axo-glial dysjunction) and migration of crucial sodium channels away from the nodal gap (Cherian et al., 1996; Sima et al., 1986, 1988), and account for the more severe nerve conduction defect in type 1 DPN.

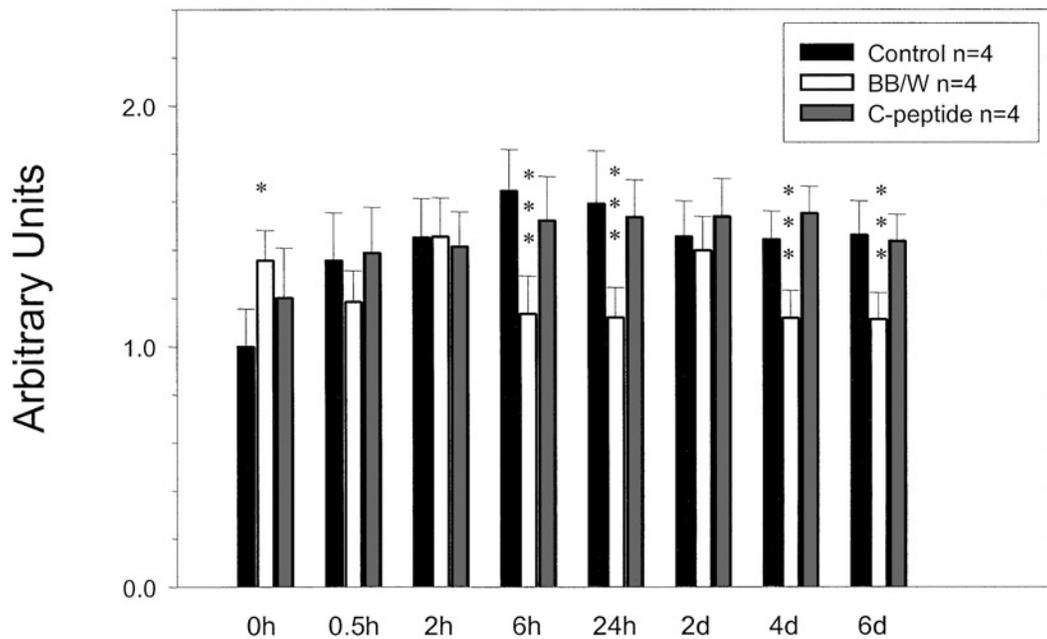
Interestingly, the insulinomimetic C-peptide prevents these changes in type 2 BB/Wor rats (Sima et al., 2000, 2001b), which we have suggested may be accounted for by the colocalization of the IR to axo-glial junctions of the paranodal apparatus and the nodal axolemma (Sugimoto et al., 2000b, 2002). Preliminary studies in our laboratory have shown that the expression or post-translational modifications of several key molecules of the paranodal apparatus, such as caspr, contactin, ankyrin_G, and sodium channel β subunits of the nodal axolemma, are significantly perturbed in type 1 BB/Wor rats but not in type 2 BB/Z rats, and that these abnormalities can be largely prevented by C-peptide (Sima et al., 2001b, unpublished data). These data strongly suggest that deficiencies of insulin itself and its "helper" C-peptide play important roles in the pathogenesis of type 1 DPN and are likely to be involved in the downstream gene regulation of several members of the IGF system, and that C-peptide replacement in this type of diabetes mellitus may provide a significant therapeutic potential in type 1 DPN.

In Vitro Studies

The effects of IGF on diabetic neuropathy have been studied in vitro in cultured superior cervical ganglia (SCG) and DRG neurons, Schwann cells, and neuroblastoma SH-SY5Y cells exposed to high concentrations of glucose or mannitol. High glucose inhibits neurite outgrowth and initiates apoptosis via activation of caspase-3 in cultured SCG and DRG neurons. The addition of IGF-I ameliorates these changes and prevents activation of caspase-3 and neuronal apoptosis (Russell et al., 1999). Similarly, Schwann cells cultured in high glucose undergo apoptosis, which is prevented by IGF-I via PI 3-kinase activation (Delaney et al., 2001).

The neuroblastoma SH-SY5Y cell system is a well-characterized in vitro model for studying neuronal development and apoptosis. Numerous studies have demonstrated that high glucose/mannitol-induced apoptosis of SH-SY5Y cells can be rescued by IGF-I (Cheng and Feldman, 1998; Matthews and Feldman, 1996; Singleton et al., 1996; van Golen et al., 2000; van Golen and Feldman, 2000). Recently, we demonstrated that glucose-induced apoptosis in SH-SY5Y cells is dose and time dependent. To separate the effect of glucose toxicity from that of hyperosmolarity, we also examined the effects of the same concentrations of mannitol on SH-SY5Y cell apoptosis.

A. IGF-1R(DRG) protein blots after sciatic nerve crush



B. β -tubulin protein (DRG) after sciatic nerve crush

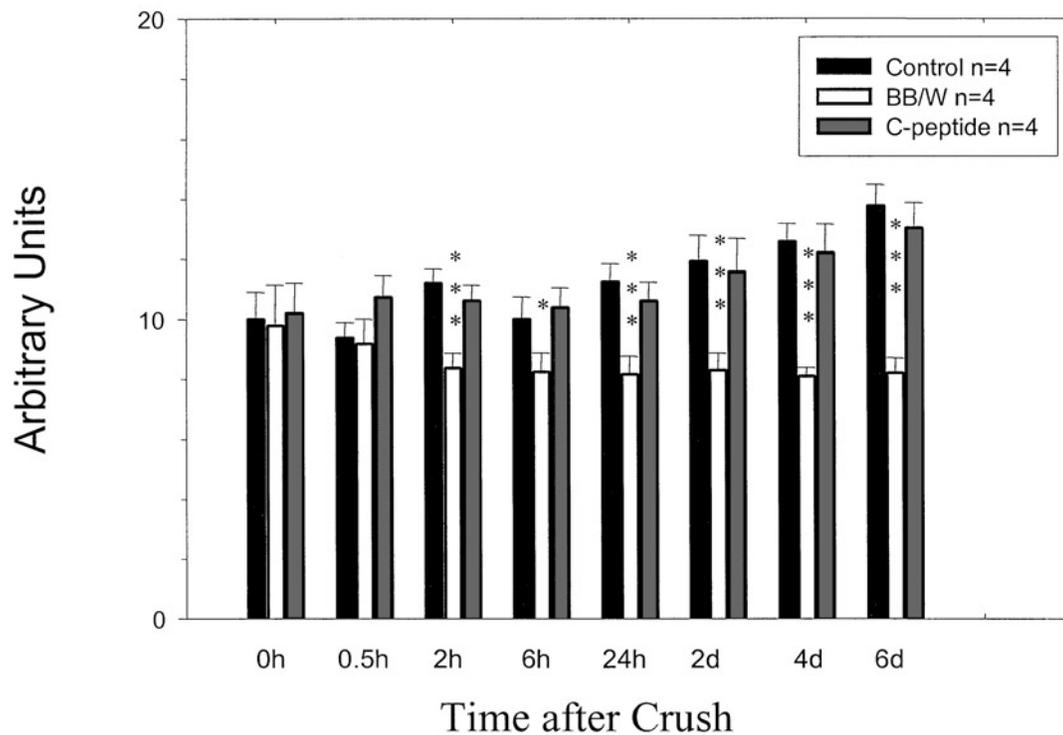


FIGURE 4

Protein expression of IGF-1R in dorsal root ganglia in type 1 diabetic BB/Wor rat and those replaced with C-peptide (A). C-peptide replacement from onset of diabetes (75 nmol/kg body weight/day) resulted in a normalization of the IGF-1R expression following sciatic nerve crush injury induced at 6 weeks of diabetes. This was accompanied by a normal expression profile of β -III tubulin (B), demonstrating that C-peptide has beneficial and normalizing effects on cytoskeletal protein expression in regenerating sensory nerve fibers in type 1 diabetes.

The extent of apoptosis induced by mannitol was significantly less than that induced by same concentration of glucose (except for extremely high concentration), suggesting that glucose toxicity per se is additive to the hyperosmolar apoptotic effects.

Our data showed that insulin (4 nM) significantly increased neurite outgrowth of SH-SY5Y cells and decreased apoptosis under high glucose concentrations. The addition of C-peptide to insulin showed further significant increases in neurite outgrowth and prevention of apoptosis. The combination of C-peptide and insulin enhanced phosphorylation of IR, but not IGF-IR, suggesting that insulin and C-peptide may signal via a common pathway. On the other hand, IGF-I showed the greatest effect on neurite outgrowth; however, the combination of IGF-I and C-peptide did not result in an additive effect on neurite outgrowth (Zhang et al., 2001, 2002).

In summary, it is well established that abnormalities of IGFs play central roles in the pathogenesis of DPN and that they impair axonal integrity and nerve fiber regeneration in DPN. These effects appear to be most expressed in type 1 diabetes, suggesting that factors other than hyperglycemia are at play. Data from our laboratory, using the proinsulin C-peptide as an insulinomimeticum, strongly suggest that insulin deficiency per se may be the major underlying culprit in the various perturbations of the IGF system. We therefore suggest that C-peptide, like insulin, be incorporated as one of the key ligands in the IGF system.

The clinical usage of IGF-I as a therapeutic agent is probably associated with several problems such as route of administration and its ubiquitous effects with potential adverse effects. Nevertheless, there are some short-term beneficial effects reported in both type 1 and type 2 patients with recombinant human IGF-I (Thraillkill, 2000). However, long-term efficacy data are lacking. Probably, a more applicable and safer approach would be to secondarily modify and correct the IGF system, particularly in type 1 diabetes, via replacement of C-peptide for instance (Sima et al., 2001b).

CNS COMPLICATION

Recent studies have provided substantial evidence that diabetes has unique impacts on the CNS. Diabetes increases stroke risk, affects glucose transport, and alters the blood-brain barrier (McCall, 1992; Mooradian, 1997). Studies in clinical and experimental diabetes suggest a variety of abnormalities in brain structure, neurotransmitters, and electrophysiology (Dejgaard et al., 1991; Jakobsen et al., 1987; Kamijo et al., 1993; Lackovic et al., 1990; Luse, 1970; Salkovic et al., 1995; Sima et al., 1992; Welsh and Wecker, 1991). The incidence of psychiatric disorders are more common in diabetic patients compared with

age-matched nondiabetic subjects (Popkin, 1997), such as major depression and phobias (Pozzessere et al., 1988). Cognitive deficits have been documented in diabetic patients, including memory retention/retrieval and complex reasoning skills (Gispén and Biessels, 2000; Helkala et al., 1995; Mooradian et al., 1988; Popkin et al., 1988; Pozzessere et al., 1988, 1991). The reasons for this may be multifold, such as a higher incidence of stroke, which also behaves differently in diabetic patients ("stroke in evolution") (Asplund et al., 1980; Fisher and Garcia, 1996; Raev, 1993; Weinberger et al., 1983), arteriosclerosis with cortical microinfarctions (Dolman, 1963; Reske-Nielsen et al., 1965), and/or diffuse white matter lesions ("leucoariosis") (Pantoni and Garcia, 1997). These changes are more common in elderly type 2 patients and are accentuated by hypertension. In contrast, repeated episodes of hypoglycemia in type 1 patients are known to cause neuronal loss in the hippocampus, cortical layers 3 and 5, and cerebellar Purkinje cells (Agardh et al., 1981; Auer et al., 1984a, 1984b), with ensuing cognitive and neurological deficits. However, Kramer et al. (1998) and Schoenle et al. (2002) reported that type 1 diabetic patients show a duration-dependent decline in cognitive function, which is unrelated to hypoglycemic episodes. Therefore, cognitive deficiency may be caused by diabetes per se. Taken together, mounting evidence support the notion that the brain is not spared from the complications of diabetes. In diabetic rats, reduction of neocortical thickness associated with neuronal loss (Jakobsen et al., 1987; Luse, 1970), decreased acetylcholine synthesis and release (Welsh and Wecker, 1991), impaired spatial memory and learning (Biessels et al., 1996; Popovic et al., 2001), and altered synaptic integrity of the hippocampus as reflected by long-term potentiation deficits (Biessels et al., 1998; Kamal et al., 2000) have been demonstrated. These animal studies also suggest that a primary encephalopathy occurs in diabetes.

The mechanisms by which diabetes causes CNS complications are not clear. Hippocampus and frontal cortex are essential parts of the limbic system and are intimately correlated with higher cognitive functions. They are vulnerable parts of the brain, with high susceptibility to ischemia and hypoglycemia. In CNS, apoptotic neuronal cell death has been described in ischemic brain injury (Kihara et al., 1994; Li et al., 1995; Linnik et al., 1993; Nitatori et al., 1995) and in neurodegenerative diseases, such as Alzheimer disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (Hartley et al., 1994; Loo et al., 1993; Offen et al., 1999; Stefanis et al., 1997; Tatton et al., 1997, 1998; Ziv and Melamed, 1998). We recently reported on a duration-dependent neuronal apoptosis in hippocampus of type 1 diabetic BB/Wor rats, which is accompanied with neuronal loss and cognitive impairments. As shown in Figure 5, perturbations of the IGF system was

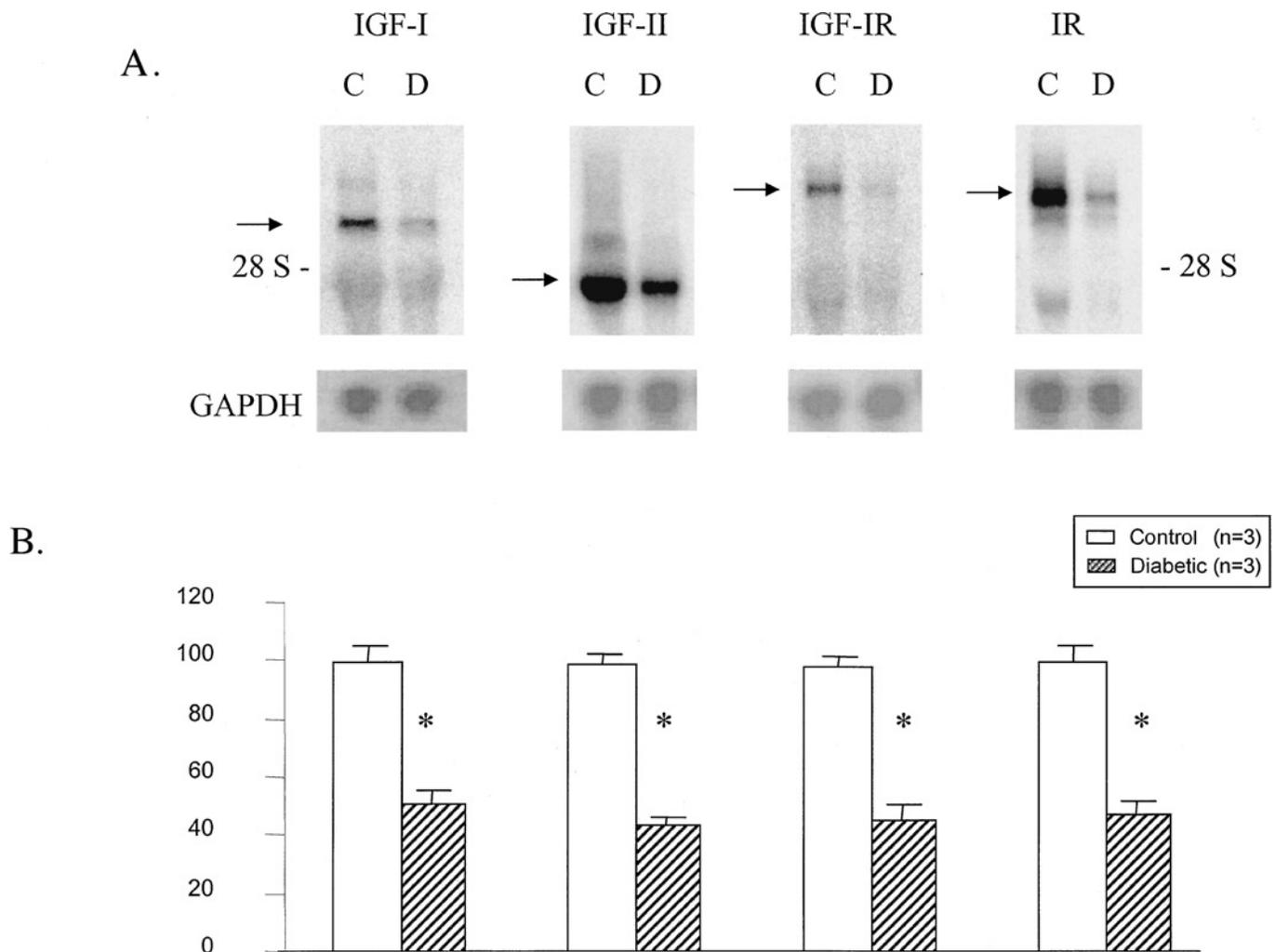


FIGURE 5

Perturbations of the IGF system in CNS in type 1 diabetic BB/Wor-rat. (A) Northern blot hybridization (representative of three blots). The mRNA levels of and IGF-I, IGF-II, IGF-IR, and IR were significantly reduced in hippocampi of 2-month diabetic BB/Wor rats compared to age-matched control rats (B). Control values are arbitrarily set to 100. Position of 28s ribosome is indicated. Arrows indicate the mRNA bands of IGF-I (7.5 kb), IGF-II (3.8 kb), IGF-IR (11 kb), and IR (11 kb) in (A). The GAPDH bands of the corresponding gel show that equal amounts of RNA was loaded onto each lane. C, control; D, diabetic.

* $P < .001$ versus control. Reproduced with permission from *Brain Research*.

demonstrated prior to the development of hippocampal apoptosis in the BB/Wor rat (Li et al., 2002a). These data suggest that neuronal apoptosis in the diabetic animals is likely to contribute to the cognitive deficiencies observed in type 1 diabetic patients. It is of interest to note that in Alzheimer disease, both IR and IGF-IR are significantly down-regulated in hippocampus (Terry et al., 2001).

IGF and the CNS Complications of Diabetes in Experimental Animals

Ishii (1995) initially proposed that decreased IGF activities may contribute to CNS alterations in diabetes. This hypothe-

sis has subsequently been supported by a series of clinical and experimental studies. Many studies show that IGF activity is impaired in the CNS of experimental diabetic animals. The expression of IGF-I and IGF-II are reduced in the spinal cord and brain of type 1 diabetic STZ and BB/Wor rats (Busiguina et al., 1996; Wuarin et al., 1994; Zhuang et al., 1997; Li et al., 2002a, 2002b) and in the spontaneously diabetic ZDF(fa/fa) (Wuarin et al., 1996). Diminished IGF-II gene expression in the brain precedes abnormalities in brain structure, neurotransmitter levels, Na^+ , K^+ -ATPase activity and learning behaviors in STZ-induced diabetes (Wuarin et al., 1996), suggesting that alterations of the IGF system exerts an important role in the

pathogenesis of CNS complications. We have used a model of type 1 diabetes, the spontaneous type 1 diabetic BB/Wor rat, to examine CNS alterations of the IGF system. In this model, IGF-I, IGF-II, IGF-IR, and IR expression was examined in 2- and 8-month diabetic animals, representing an early and a chronic state of diabetes. In both 2-month and 8-month diabetic animals, the expression of IGF-I and IGF-II, IGF-IR, and IR were significantly reduced compared to age-matched control rats, suggesting that the IGF system is impaired at the early stage and continues to decline with disease progression (Li et al., 2002a). The early impairments of the IGF system preceded significant apoptosis and neuronal cell loss in the CA₁ region of the hippocampus, which became evident only at 8-month duration of diabetes. Apoptotic activity correlated with deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL) staining, DNA laddering, caspase-3 activity, and Bax/Bcl_x expression. Spatial learning and memory were significantly impaired in diabetic animals (Li et al., 2002a). These results indicate a duration-dependent IGF-associated neuronal apoptosis leading to cognitive dysfunction. Interestingly, C-peptide replacement corrected partially but significantly the abnormalities in IGF-I, IGF-II, IGF-IR, and IR expression in the hippocampus and partially prevented hippocampal apoptosis, neuronal loss, and the functional cognitive impairment (Li et al., 2002b).

In STZ-diabetic rats, insulin treatment prevents water maze learning and hippocampal impairments of long-term potentiation (Biessels et al., 1998), and reverses the prolonged latencies of auditory and visual evoked potentials (Biessels, 1999). These results suggest that insulin deficiency may play a crucial role in impaired CNS function in type 1 diabetes. Because insulin replacement therapy partially restores IGF-II mRNA levels in the cerebral cortex and spinal cord in the same animal model (Wuarin et al., 1996), insulin may exert its role via activation of the IGF system, which would be consistent with the same effects of the insulinomimetic C-peptide.

In Vitro Studies

In cerebrocortical and cerebellar granule cell cultures, IGF-I significantly reduces cell death induced by glucose deprivation (Harper et al., 1996). Two IGF analogues: QAYL and B-chain mutants, which show reduced affinity for IGF-BPs, are as effective as IGF-I in promoting cell survival in conditions of glucose deprivation, indicating that IGF-I promotes neuronal survival. Apoptosis of cerebellar granule cells is blocked by IGF-I (Galli et al., 1995). Preliminary data from our laboratory suggest that primary hippocampal neurons grown in high glucose are protected from apoptosis by either IGF-I, insulin, or C-peptide (Li et al., unpublished data).

DIFFERENCE IN IGF ACTIVITIES IN THE CNS AND PERIPHERAL NERVE SYSTEM (PNS)

The alterations in IGF activities differ in peripheral nerve from those in the central nervous system in both STZ-diabetic rats and BB/Wor rats. The neurophysiological abnormalities of peripheral nerve usually occur more rapidly than those of the central nervous system (Biessels, 1999; Kamiyo et al., 1993; Li et al., 2002b; Sima et al., 1992).

The patterns of decline in the IGF system are different in PNS and CNS in type 1 diabetic BB/Wor rats. IGF perturbations are established in peripheral nerves at 6-week duration of diabetes, whereas this is only evident at 2-month duration of diabetes in the hippocampus. Furthermore, in CNS of diabetic BB/Wor rats, IGF-I, IGF-II, IGF-IR, and IR are decreased at both the mRNA and protein levels (Li et al., 2002a), whereas in the peripheral nerve of the same model, IGF-I and IGF-II expression is reduced, but IR and IGF-IR expression are increased (Sugimoto et al., 2000b; Xu and Sima, 2001). These data suggest that insulin deficiency may involve different mechanisms by which the IGF system is regulated in the PNS versus the CNS.

CONCLUSIONS AND FUTURE DEVELOPMENTS

More than 15 years of fairly extensive experimental research and limited clinical research have established the IGF system and its perturbations as important pathogenetic factors in the development of the neurological complications, particularly those associated with type 1 diabetes. There is strong evidence to suggest that abnormalities in IGF metabolism occur independently of hyperglycemia and that they are linked to insulinopenia. Limited clinical trials have indicated that restoration of IGF activities may prevent or even to some extent reverse neurological deficits associated with diabetes. However, the ubiquity of IGF activities poses a challenge to target specific tissues, even within the nervous system, because the perturbations of various gene responses of IGFs in the CNS and the PNS divert in opposite directions.

There is evidence to suggest that insulin and the proinsulin C-peptide play important roles in regulating and correcting the diverse aberrations of IGFs. Hence, a logical conjecture of these relationships would be to replenish the insulinomimetic C-peptide in parallel to optimal insulin treatment. In fact several short-term clinical trials have underlined the beneficial effects of C-peptide on several chronic complications, which are in keeping with the experimental data. However, a major obstacle and challenge is to find support for large scale Food and Drug Administration (FDA)-approved clinical trials testing the efficacy of C-peptide in diabetic complications. Because patents on C-peptide are long expired, the incentives on part of the

industry to provide the peptide and funds for necessary trials are nonexistent. This stumbling block needs to be overcome by National Institutes of Health (NIH) mechanisms or by support from nonprofit organizations to initiate appropriately designed clinical trials. A potential but distant possibility is the developments within the human genome research projects targeting not only IGF-I itself, but also related peptides such as C-peptide or others. However, these possibilities are to the best of the knowledge not yet in the plans.

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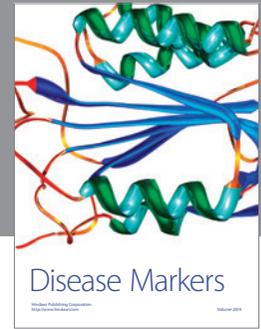
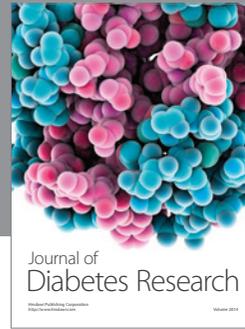
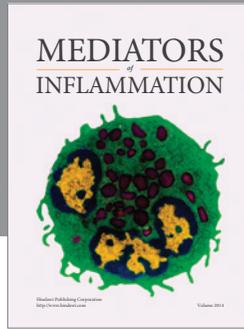
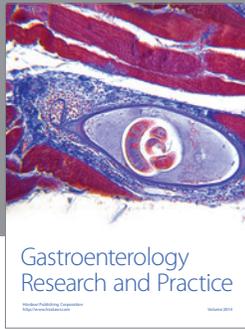
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