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# Signaling by insulin-like growth factor 1 in brain

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**Abstract**

The homologous insulin and insulin-like growth factor (IGF) receptors are both expressed in the brain, in overlapping but distinct neuroanatomical patterns. In contrast to insulin, IGF1 is also highly expressed within the brain and is essential for normal brain development. IGF1 promotes projection neuron growth, dendritic arborization and synaptogenesis. IGF1 acts in an autocrine and/or paracrine manner to promote glucose utilization, using phosphatidylinositol 3 kinase (PI3K)/Akt, also known as protein kinase B (PKB)/glycogen synthase kinase 3β (GSK3β) pathways similar to insulin signaling in peripheral tissues. IGF1 promotes neuronal survival during normal brain development mainly in hippocampal and olfactory systems that depend on postnatal neurogenesis. IGF1's anabolic and neuroprotective roles may be coordinated by inhibition of GSK3β. The identification of GSK3β as a major target of brain IGF1 signaling provides a unifying pathway for IGF1's well-established anabolic and anti-apoptotic functions, with IGF1-induced inhibition of GSK3β triggering multifaceted anabolic and neuroprotective effects.


*Keywords:* Insulin; Metabolism; Akt; GSK3β (Glycogen synthase kinase 3β); Tau; Ketogenic diet

## 1. Insulin and IGF1

Insulin and insulin-like growth factor (IGF) 1 are genetically related polypeptides that have similar tertiary structures and substantial amino acid identity. Insulin is synthesized predominantly in pancreatic beta cells from which its release is regulated by nutrient stimuli. IGF1 is made in great abundance by the liver where its synthesis is stimulated by pituitary growth hormone (GH). IGF1 is also synthesized locally in many tissues, including the brain, where GH does not regulate its synthesis to any major degree. Circulating insulin levels peak after meals but are normally very low most other times; in contrast, circulating IGF1 levels are high and stable around the clock. Also in contrast to insulin, IGF1 in the circulation and in tissues is bound to high affinity IGF binding proteins (IGFBPs) (Duan, 2002). This binding is thought to prolong IGF1 half-life by impeding proteolysis and to modulate the peptide's interaction with the IGF1 receptor.

## 2. Insulin and IGF1 receptors

Like the cognate peptides, the insulin and IGF1 receptors (Fig. 1) demonstrate close structural homology and sequence identity (LeRoith, 1996). Insulin and IGF1 bind their cognate receptors with highest affinity, but cross-reactivity occurs at higher hormone concentrations. The insulin and IGF1 receptors are receptor tyrosine kinases (RTK) that, after ligand binding induced autophosphorylation, associate with insulin receptor substrate (IRS) adapter proteins. These IRS proteins bind to tyrosine phosphate docking sites on the activated receptors, undergo phosphorylation themselves, and then recruit additional SH2 signaling proteins to transduce insulin or IGF1 actions. A number of immediate second messengers have been implicated in insulin/IGF1 action, including phosphatidylinositol 3 kinase (PI3K), growth factor receptor bound protein 2 (GRB-2), SH2-containing phosphatase-2 (SHP-2), GTPase activating protein (GAP), and phospholipase C-γ (PLC-γ), among others. This review focuses on the PI3K pathway, which has been specifically elucidated in IGF signaling in the brain.

While insulin functions primarily as an immediate response hormone to promote nutrient uptake and utilization by peripheral tissues and to control systemic blood glucose

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level, IGF1 has a more sustained role in promoting anabolic growth and homeostasis of the musculoskeletal and nervous systems. Given the similar signaling mechanisms of these ligands at their cognate receptors, the explanation for their distinct biological roles may involve the regulation of peptide access to its receptor and cell- and developmental stage-specific expression patterns of ligands and receptors. Thus, to elucidate the roles of insulin and IGF1 in the brain, we investigate the expression of their receptors and the availability of the ligands.

Both the insulin and IGF1 receptors are widely expressed in the brain and are concentrated in neuron rich structures (Fig. 2). This has been shown by in situ hybridization identifying the cells synthesizing the receptor proteins (Bondy et al., 1992a,b) and by ligand binding studies (Bohannon et al., 1988; Hill et al., 1986), showing the sites of membrane receptor expression. There is extensive overlap and indeed co-expression of these receptors in many brain regions, such as the granule cell layers of the olfactory bulb, hippocampal formation and cerebellar cortex (Bondy et al., 1992a). Superimposed on this generalized pattern there are also distinct cell populations exhibiting selective enrichment for insulin or IGF1 receptor expression. For example, the insulin receptor is highly expressed in anterior thalamic and hypothalamic nuclei, including the periventricular, reticular and anterior thalamic nuclear complex and the paraventricular and supraoptic nuclei. IGF1 receptor expression is selectively concentrated in the suprachiasmatic nucleus of the hypothalamus and in dorsal thalamic sensory nuclei, as illustrated in Fig. 2 (Bondy et al., 1992a,b). Interestingly, while both receptors are localized in Ammon's horn, the insulin receptor is selectively enriched in CA1 while the IGF receptor is most prominent in CA3 (Bondy et al., 1992a).

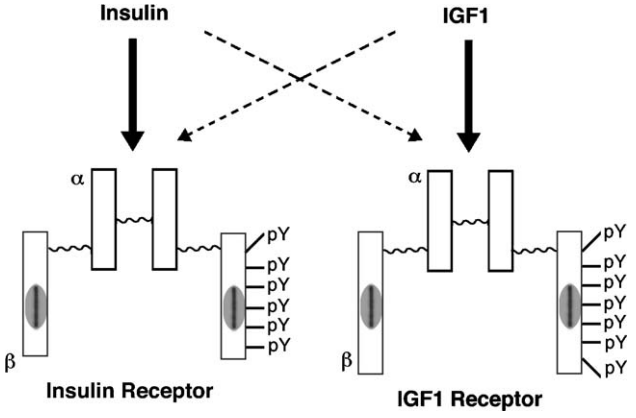


Fig. 1. Structural homology between insulin and IGF1 receptors. The receptor tyrosine kinases are intrinsic membrane proteins. The extracellular, disulfide linked, ligand-binding alpha subunits of insulin and IGF1 receptors are ~ 70% identical and exhibit 10-fold greater affinity for the cognate ligand, but, as indicated by the dashed arrows, each receptor competitively binds the related peptides. The signal transducing largely intracellular beta-subunits share a high degree of amino acid sequence identity, particularly in the tyrosine kinase domain (shaded area). The distribution of tyrosine phosphorylation sites is indicated (pY). The IGF1 receptor has a slightly longer carboxy-terminal domain with an additional pY site not found in the insulin receptor. This is the only apparent difference in receptor structure that suggests potential divergence in substrate specificity.

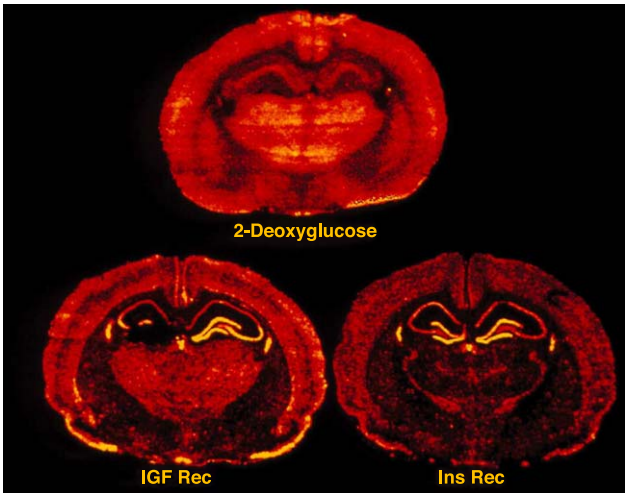


Fig. 2. Brain [$^{14}$C]-2-deoxyglucose uptake compared with IGF1 and insulin receptor expression. The figure shows color-coded, digitized autoradiographs comparing [$^{14}$C]-2-deoxyglucose uptake with IGF1 receptor and insulin receptor gene expression in serial brain section. Neuroanatomical patterns of glucose utilization closely reflect IGF1 but not insulin receptor expression.

## 3. Insulin and IGF1 in brain

### *3.1. Sources of brain insulin and IGF1*

Circulating insulin and IGF1 may influence hypothalamic neurons by interacting with receptors localized in the median eminence and circumventricular structures outside the blood–brain barrier. Both insulin and IGF1 receptors are expressed on brain capillaries, but IGF1 crosses the blood–brain barrier with significantly greater efficiency than insulin (Reinhardt and Bondy, 1994). After intra-carotid infusion of radiolabeled ligands, 3–4-fold more IGF1 is detected within isocortical parenchyma, and almost 10-fold more is concentrated in the hypothalamus (Reinhardt and Bondy, 1994). It has been suggested that IGFBPs that are abundantly expressed along the blood–brain barrier (Lee et al., 1993) may facilitate IGF1 transit into the brain (Reinhardt and Bondy, 1994).

Very little insulin is synthesized within the brain (Coker et al., 1990), although small foci of insulin mRNA are detected in the anterior hypothalamus (Young, 1986). In contrast, IGF1 mRNA is abundant in the brain, especially during postnatal development (Bartlett, 1959; Bondy, 1991) and in response to injury (Lee and Bondy, 1993). IGF1 mRNA is most abundant in growing projection neurons in sensory and cerebellar relay systems (Bondy, 1991) and the

IGF1 receptor is highly expressed in the same neurons (Bondy et al., 1992b), suggesting an autocrine or paracrine mode of action.

### 3.2. IGF1 has insulin-like effects in the brain

Regional glucose utilization as measured by [$^{14}$C]-2-deoxyglucose uptake parallels IGF1 and IGF1 receptor gene expression in the developing murine brain (Fig. 2 and (Cheng et al., 2000)). High level IGF1 expression is seen in concert with intense [$^{14}$C]-deoxyglucose uptake in maturing cerebellar, somatosensory, auditory-vestibular, olfactory and visual system neurons. IGF1 and other elements of the IGF system are strongly induced in response to diverse types of central nervous system (CNS) injury. Interestingly, this injury-invoked IGF1 expression is generally in astrocytes (Gehrmann et al., 1994; Komoly et al., 1992; Lee et al., 1992; Li et al., 1998), where it is also strongly correlated with local [$^{14}$C]-2-deoxyglucose uptake (Cheng et al., 2000). Glucose utilization is reduced by ~30–60% in the developing IGF1 null brain, with the greatest decrease in structures where IGF1 expression is normally highest (Cheng et al., 2000). The defect in glucose utilization in IGF1 null brains is demonstrable at the nerve terminal level (synaptosomes) in vitro, and is completely reversed by IGF1. These in vitro findings show that the defect in glucose utilization seen in the IGF1null brain in vivo is not due to reduced neural activity or reduced brain blood flow, neither of which affects the synaptosome preparation. Furthermore, the finding of reduced glucose uptake in isolated neuron terminals shows that IGF1 normally promotes glucose uptake by terminals independent of glial effects, since glia are not present in the synaptosome fraction.

IGF1 deficiency results in decreased postnatal brain growth (Beck et al., 1995; Cheng et al., 2000). This effect is clearly more profound in the nullizygous state, but even partial IGF1 deficiency, as in IGF1 +/− mice, results in significantly diminished brain growth. Even though these mice are not significantly smaller in body size than wild-type (Wang et al., 1999), the heterozygous brains are ~10% smaller than wild-type (WT) at P40 ($P < 0.0001$) (Cheng et al., 2000). Despite the reduction in size, IGF1 null brain anatomy and cell numbers are for the most part normal, with the notable exceptions of the dentate gyrus and the olfactory bulb (Beck et al., 1995; Cheng et al., 1998). Most of the 30–40% reduction in brain size in adult IGF1 null mice is due to a reduction in cell size and neuropil, or neuronal processes. Cell density is significantly increased in the IGF1 null brain (Fig. 3 and Beck et al., 1995; Cheng et al., 1998, 2003b), suggesting decreased process growth, since the space between neurons is normally occupied by extensively branched neuronal processes. Soma size of projection neurons in the IGF1 null brain is reduced by ~25%, and dendritic length, branching and synapses are reduced by a similar amount (Fig. 3 and Cheng et al., 2003b). Thus it appears that impaired neuronal somatic growth and process formation accounts in large part for the reduction in IGF1 null brain size. Supporting these in vivo findings, a recent study reported that IGF1 treatment significantly increased dendritic growth of cortical slices (Niblock et al., 2000).

### 3.3. IGF1 activates insulin-like signaling pathways in brain

In peripheral tissues, insulin receptor activation triggers a kinase cascade leading through phosphatidylinositol 3-kinase (PI3K) to phosphorylation of protein kinase B/Akt

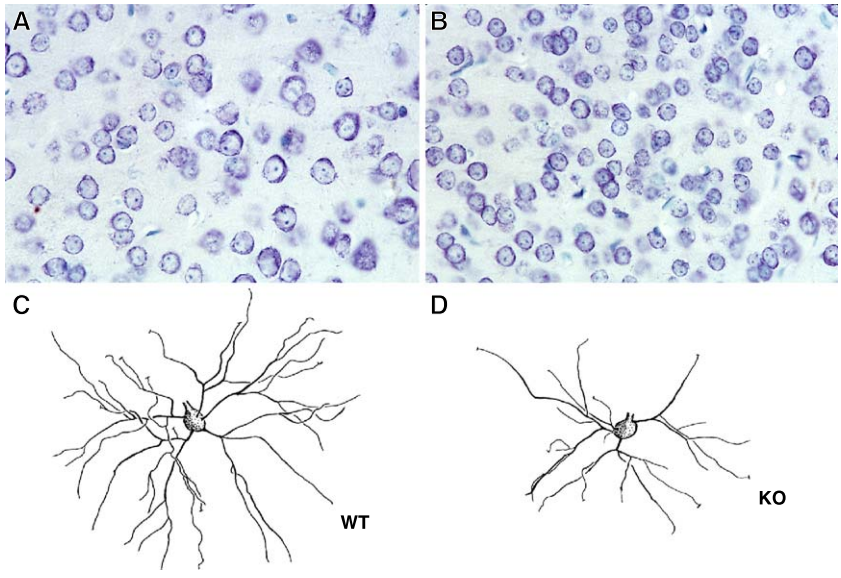


Fig. 3. Cortical neuron density and dendritic profiles in adult WT (A, C) and IGF1 null mice (B, D). Representative toluidine blue-stained sections from the frontoparietal cortex of P50 mice (A and B) show reduced somatic size and increased cell density in IGF1 null mice. Camera lucida drawings of Golgi-stained cortical pyramids (layers II–III) reveal dramatically reduced dendritic profiles of the IGF1 null neuron (C and D). Adapted from Cheng et al. (2003b).

(Summers and Birnbaum, 1997). Activation of this kinase leads to translocation of facilitative glucose transporters (GLUTs), from intracellular pools to the plasma membrane, promoting glucose entry into cells (Kohn et al., 1996; Summers and Birnbaum, 1997). The active, phosphorylated form of this kinase (phospho-serine$^{473}$ and -threonine$^{308}$ Akt) is concentrated in granular deposits in IGF1-expressing neuronal processes in WT brains, but is barely detectable in these same neurons in IGF1 null brains (Cheng et al., 2000). In the WT brain, GLUT4 immunoreactivity is concentrated in the processes of IGF1-expressing neurons in a pattern similar to phospho-Akt, suggesting a physical association of these proteins in translocation of GLUT4 to the plasma membrane. In IGF1 null brains, however, GLUT4 immunoreactivity is reduced and largely confined to perikarya. GLUT4 mRNA is also decreased in IGF1 null projection neurons(Cheng et al., 2000). Thus, IGF1-induced Akt phosphorylation appears linked to both production and translocation of neuronal GLUT4 from intracellular pools to nerve process membranes in the normal developing brain. Changes in GLUT1 and GLUT3 mRNAs were not detected in IGF1 null brains and investigations of differences in subcellular localization of these two transporters were inconclusive. Hexokinase activity is significantly reduced in IGF1 null brains, suggesting a role for IGF1 in regulation of brain hexokinase activity, which may also contribute to the decreased glucose utilization in the IGF1 null brain (Cheng et al., 2000).

Another target of insulin/IGF signaling via Akt/protein kinase B (PKB) is glycogen synthase kinase 3β (GSK3β). Insulin and IGF1 have both been shown to stimulate the inhibitory serine phosphorylation of this pivotal enzyme in cultured neurons (Hong and Lee, 1997). Insulin/IGF-induced inhibitory phosphorylation of GSK3β on serine$^{9}$ (Summers et al., 1999) relieves GSK3β's inhibition of glycogen synthase and the translation initiation factor eIF2B, thus promoting glycogen and protein synthesis. Observations in IGF1 null mice provide compelling evidence that GSK3β is involved in anabolic pathways in brain development (Cheng et al., 2000). Immunoreactivity specific for Ser$^{9}$-phospho-GSK3β is selectively concentrated in the perikarya of large, IGF1-expressing projection neurons in WT brain, associated with abundant glycogen accumulation in the same neurons (Fig 4). In the IGF1 null brain, however, Ser$^{9}$- phospho-GSK3β is barely detectable, and glycogen stores are profoundly reduced (Fig. 4). The colocalization of phospho-GSK3β with abundant glycogen stores specifically in IGF1-expressing neurons suggests that IGF1 acts in an autocrine manner to promote glucose uptake and storage as glycogen in developing projection neurons. Interestingly, while glycogen is associated with astrocytes in the mature brain, neuronal glycogen synthesis is abundant in postnatal development during the time of peak IGF1 expression (Bondy, 1991; Borke and Nau, 1984). Another important GSK3β target is the translation initiation factor eIF2B (Frame and Cohen, 2001). We did not evaluate eIF2B in this study, but predict that it too would be inhibited by GSK3β overactivity, contributing to the asthenia affecting IGF1 null neurons.

Tau, a microtubule associated protein involved in neurofilament stabilization, is a GSK3β substrate. In vitro studies have shown that both insulin and IGF1 inhibit GSK3β in neural cells resulting in tau-hyperphosphorylation (Hong and Lee, 1997; Lesort and Johnson, 2000). When hyperphosphorylated, tau is prone to form intracelllular neurofibrillary tangles that contribute to neuronal degeneration. We have found that tau phosphorylation is increased in the IGF1 null brain compared to WT littermates (Fig. 5). The finding

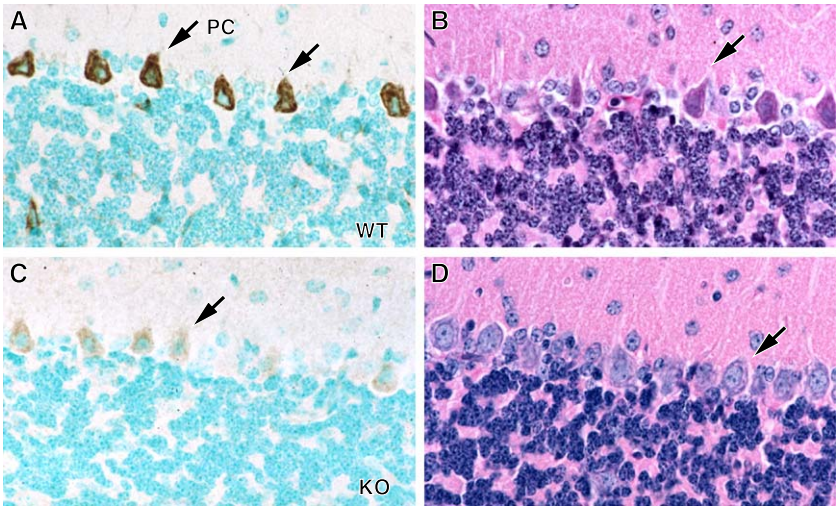


Fig. 4. Phosphorylation of glycogen synthase kinase 3β (GSK3β) and glycogen synthesis in WT (A and B) and IGF1 null (C and D) cerebellar cortex. The brown immunostain in A and C represents Ser$^{9}$-phosphorylated GSK3β, which is selectively concentrated in IGF1-expressing projection neurons in WT brains and is barely detectable in IGF1 null brain. Likewise, glycogen (the purple PAS stain in B, D) is abundant in WT but barely detected in IGF1 null Purkinje cells (PC). Adapted from Cheng et al. (2000).

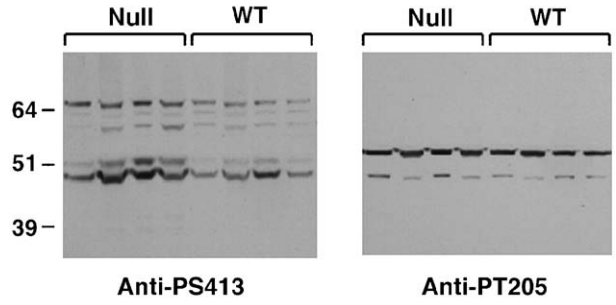


Fig. 5. Immunoblot analysis of anti-tau PS413 (A) and anti-tau PT205 (B) on total membrane fractions prepared from IGF1 null and WT brains. (A) Three major protein bands with molecular weights ~ 65, 51 and 48 kDa detected by anti-tau PS413, which recognizes the GSK3β-specific phosphorylation site. All are significantly increased in IGF null brains ($P = 0.0003$, 0.01, 0.04, respectively). (B) The membrane was stripped and re-probed with anti-tau PT 205, which specifically recognizes a cyclin-dependent kinase 5/p23 phosphorylation site. There was no significant difference in signal for this tau phosphorylation form in IGF1 null and WT brains.

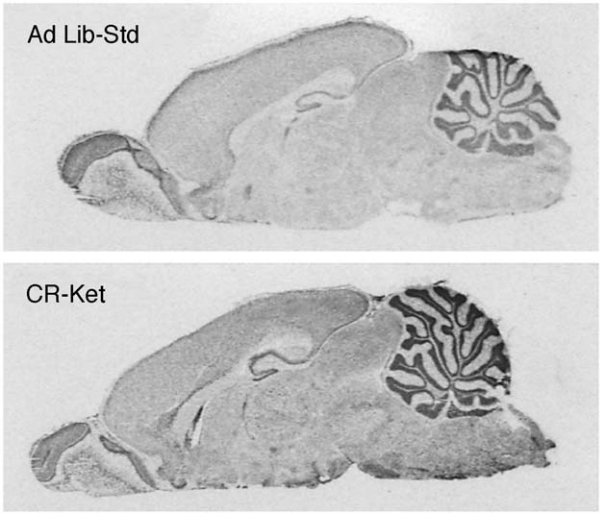


Fig. 7. Augmentation of IGF1 receptor gene expression by the ketogenic diet. These are film autoradiographs showing IGF1 receptor mRNA in representative sagittal sections from rats on a standard rat chow, ad lib diet (top) versus a low-carbohydrate, high lipid, ketogenic diet (below). The rats were on the diet for 7 days. Adapted from Cheng et al. (2003a).

of tau hyperphosphorylation is another piece of evidence suggesting that IGF1-induced inhibition of GSK3β is a central mechanism of IGF1 action in brain. Interestingly, GSK3β appears to promote apoptosis in neurons (Crowder and Freeman, 2000; Hetman et al., 2000; Li et al., 2000; Tong et al., 2001), possibly through hyperphosphorylation of tau and β-catenin (Lucas et al., 2001). Thus, GSK3β hyperactivity in the IGF1 null brain may contribute not only to hypoplastic neuronal development through reduced anabolic processes but also to increased neuronal loss, as seems to occur in the dentate gyrus (Cheng et al., 2001). The signaling pathways implicated in IGF1 actions within the brain are diagramed in Fig. 6.

## 4. Regulation of brain IGF system expression

While it has been known for many years that IGF1 production in the liver and in some peripheral tissues is regulated by GH, there is virtually no understanding of factors regulating brain IGF1 expression. Nor is there any information on the regulation of brain IGF1 receptor or

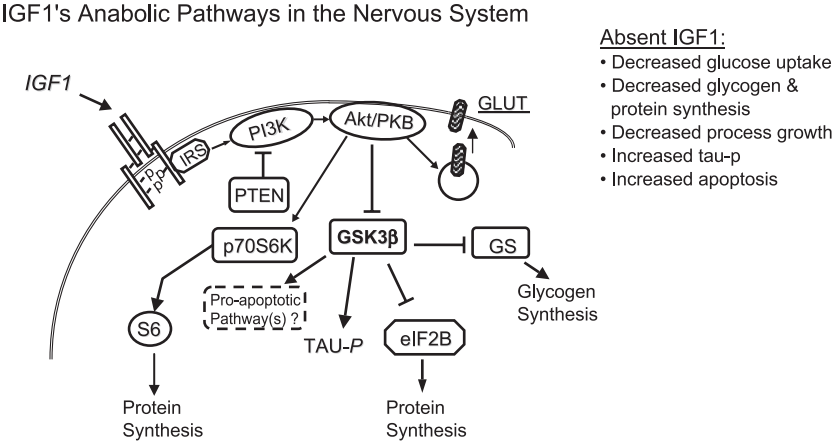


Fig. 6. Illustration of molecular pathways implicated in IGF1 and insulin signaling in the brain. IGF1 binding to the IGF1 receptor triggers receptor autophosphorylation and association with IRS docking proteins. Phosphatidylinositol 3 kinase (PI3K) is then activated and generates phospholipids which activate Akt/PKB. Akt/PKB promotes translocation of GLUTs (1, 3 and 4) from intracellular endosomal pools to the plasma membrane, thus augmenting glucose transport into the cell. Akt/PKB also serine phosphorylates GSK3β, causing inhibition. Since GSK3β normally inhibits glycogen synthase and eIF2b, inactivation of GSK3β promotes both glycogen and protein synthesis. The microtubule associated protein tau is also a target for GSK3β and is hyperphosphorylated in the IGF1 null brain, providing further evidence that IGF1 normally inhibits brain GSK3β activity. Finally, GSK3β has been implicated as a pro-apoptotic factor in neurons, so this pathway may be involved in IGF1's neuroprotective effects as well.

IGFBP expression. Because the insulin/IGF system is generally responsive to nutritional status (Calikoglu et al., 2001; Thissen et al., 1994), we investigated the effects of modest caloric restriction and alteration of dietary macronutrient composition on brain IGF system gene expression. The model we chose to investigate has clinical importance, in that the lipid-based, ''ketogenic'' diet is used to treat children with refractory epilepsy (Swink et al., 1997). We found that diet has important and complex effects on brain IGF system and glucose transporter gene expression (Cheng et al., 2003a). A modest, ~ 10% calorie restriction reduced brain IGF1 and IGF1 receptor mRNA levels in rats on a standard, carbohydrate dominant diet, with no appreciable effect of this dietary manipulation on brain IGFBP or glucose transporter gene expression. A diet with the same calorie content composed primarily of lipid, however, increased brain IGF1 receptor (Fig. 7), IGFBP3 and glucose transporter mRNA levels (Cheng et al., 2003a). Since serum and presumably brain ketone levels were greatly increased on the ketogenic diet, we propose that ketones may directly or indirectly augment brain IGF1 receptor expression, and that given IGF1's neurotrophic activity, this effect may be instrumental in the ketogenic diet's neuroprotective effects.

## 5. Conclusions

Brain glucose utilization is usually viewed as a barometer of neural activity, but neurons also require glucose to support growth, repair and remodeling processes. We have reviewed evidence that IGF1 promotes brain anabolic activity resulting in increased neuronal survival, process growth and synaptogenesis during early postnatal development. It appears that IGF1 promotes neuronal growth and dendritogenesis by 'insulin-like' anabolic effects on glucose utilization and protein synthesis, ensuring the huge biosynthetic needs accompanying this growth. IGF1 promotes activation of protein kinase B/Akt, leading to enhanced GLUT4 expression and surface membrane localization in growing projection neurons. IGF1 inhibits glycogen synthase kinase 3β (GSK3β), thereby augmenting glycogen and protein synthesis in IGF1-expressing neurons. Inhibition of GSK3β may also mediate IGF1's neuroprotective role, since GSK3β has pro-apoptotic effects on neurons.

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