Integrating insulin-like growth factor 1 and sex hormones into neuroprotection: Implications for diabetes

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Abstract

Brain integrity and cognitive aptitude are often impaired in patients with diabetes mellitus, presumably a result of the metabolic complications inherent to the disease. However, an increasing body of evidence has demonstrated the central role of insulin-like growth factor 1 (IGF1) and its relation to sex hormones in many neuroprotective processes. Both male and female patients with diabetes display abnormal IGF1 and sex-hormone levels but the comparison of these fluctuations is seldom a topic of interest. It is interesting to note that both IGF1 and sex hormones have the ability to regulate phosphoinositide 3-kinase-Akt and mitogen-activated protein kinases-extracellular signal-related kinase signaling cascades in animal and cell culture models of neuroprotection. Additionally, there is considerable evidence demonstrating the neuroprotective coupling of IGF1 and estrogen. Androgens have also been implicated in many neuroprotective processes that operate on similar signaling cascades as the estrogen-IGF1 relation. Yet, androgens have not been directly linked to the brain IGF1 system and neuroprotection. Despite the sex-specific variations in brain integrity and hormone levels observed in diabetic patients, the IGF1-sex hormone relation in neuroprotection has yet to be fully substantiated in experimental models of diabetes. Taken together, there is a clear need for the comprehensive analysis of sex differences on brain integrity of diabetic patients and the relationship between IGF1 and sex hormones that may influence brain-health outcomes. As such, this review will briefly outline the basic relation of diabetes and IGF1 and its role in neuroprotection. We will also consider the findings on sex hormones and diabetes as a basis for separately analyzing males and females to identify possible hormone-induced brain abnormalities. Finally, we will introduce the neuroprotective interplay of IGF1 and estrogen and how androgen-derived neuroprotection operates through similar signaling cascades. Future research on both neuroprotection and diabetes should include androgens into the interplay of IGF1 and sex hormones.

Key words: Diabetes; Androgens; Estrogen; Insulin; Insulin-like growth factor 1; Neuroprotection; Brain
INFORMATION

Diabetes mellitus is a metabolic syndrome known for impaired insulin production. This condition is associated with an abundance of sequelae including cardiovascular disease, brain atrophy, and more recently, Alzheimer’s disease. Over the past thirty years, researchers have established strong evidence supporting a link between patients with diabetes and subsequent cognitive impairments and abnormalities in brain integrity.

While meta-analyses have found inconsistencies in the specifics of the literature, general trends point to cognitive impairments and abnormalities in related structural and functional brain areas. For example, patients with type 1 diabetes (T1D) are frequently found to have decreased psychomotor speed, mental flexibility, and IQ scores. T1D patients also often show reductions in the volume of regional gray matter in areas such as the prefrontal cortex, hippocampus, and thalamus. On the other hand, affected skills in type 2 diabetes (T2D) are largely executive function, memory, and information processing. Neuroimaging studies done on T2D patients indicate global brain atrophy and microstructural changes, while findings regarding white matter hyperintensities are mixed.

In both T1D and T2D these decrements are considered mild across most age groups. The severity of cognitive impairments and brain abnormalities are correlated with age of onset in T1D and duration of the disease in T2D. Age is also a risk factor as deficits in learning and memory have been reported to worsen considerably in T2D patients above 65 years of age. Findings suggest the decreased brain volume in patients with T2D is correlated with increased insulin resistance, and both brain atrophy and microstructural changes are associated with impaired cognitive performance.

These data lend support to the idea that brain integrity is compromised in patients with both T1D and T2D, but also emphasize the need to integrate peripheral biomarkers associated with neuroprotection into diabetes research in humans. Various hormones altered as a result of diabetes have been recognized as neuroprotective, including insulin-like growth factor 1 (IGF1) and sex hormones. Research has revealed differences in the serum levels of IGF1 and gonadal hormones in diabetic patients, with clear sex differences in the effects of androgens and estrogens on the brain in animal models.

There is currently a movement in biomedical research to incorporate analyses of sex differences into studies; however, studies on brain integrity of diabetic patients often fail to examine men and women separately. This is despite findings of sex-specific differences in regional brain volume between men and women. Others have shown that, by combining the data of men and women, T2D patients had smaller gray matter volume with larger ventricular volume and white matter lesions compared to healthy controls. However, when the sexes were analyzed separately, the data for men failed to reach statistical significance.

Because sex hormones can act on similar molecular pathways as IGF1, and IGF1 is functionally related to insulin and diabetes, there is a need to further investigate how these hormones interact in the brains of diabetic patients. The relationship between estrogen and IGF1 is the most extensively studied in the neuroprotection literature, but it has yet to expand experimentally into diabetes research. Furthermore, little attention has been paid to androgen-IGF1 interactions, even in the animal literature, despite the similar mechanisms underlying estrogenic and androgenic neuroprotection.

DIABETES AND IGF1 RELATION

IGF1 has a hypoglycemic response similar to insulin and, in some circumstances, is capable of modulating insulin receptor (IR) activities. Research has demonstrated that low IGF1 is associated with T1D and T2D. Moreover, genetic studies suggest decreased IGF1, due to a genetic polymorphism in the promoter region of the IGF1 gene, increases the risk of glucose intolerance and T2D.

On the other hand, T2D has also been correlated...
with excessively high levels of IGF1. For example, people with acromegaly - a condition known for its overproduction of pituitary growth hormone - have both high levels of IGF1 and a greater risk of developing T2D[49]. These findings were corroborated by two large studies from Denmark (n = 3354) and Germany (n = 7777) which found U-shaped associations between IGF1 levels and the likelihood of developing insulin resistance and T2D[24,25]. Moreover, treatment with IGF1 can improve glycemic control in patients with T1D and T2D[43,46], which may suggest an optimal range of IGF1 for normal glycemic control.

Although IGF1 is synthesized in the brain, peripheral values cannot be used to accurately infer brain levels of IGF1 in humans as local synthesis of IGF1 in the brain appears not to correlate with the quantity of IGF1 receptors (IGF1R)[47-49]. Evidence from animal models suggest that brain atrophy and loss of DNA are prevented following injection of insulin and IGF1, but not insulin alone, into cerebrospinal fluid of mice[50]. Thus, proper systemic levels of IGF1 and its transport from the periphery into the brain is likely necessary for the maintenance of various cognitive processes[51].

Collectively, these data support the involvement of IGF1 in diabetes but also point to an “optimal range” of IGF1. Future research should examine the significance of an optimal peripheral range in the development and maintenance of diabetes and cognitive decline. Moreover, there is a need for data on the role of central vs peripheral IGF1 levels and the subsequent impact on cognitive impairment and brain atrophy.

**THE IGF1 SYSTEM**

**Transportation**

IGF1 is a polypeptide, structurally similar to insulin, that is released in response to growth hormones secreted by the anterior pituitary[52]. While synthesized predominantly by hepatocytes in the liver and released into general circulation, both paracrine and autocrine functions contribute through local tissue synthesis of IGF1. The concentration of IGF1 is greatest during perinatal development and decreases markedly into adulthood. IGF1R are expressed in nearly all neural cells of the CNS, being most highly expressed in the cortex, hippocampus, cerebellum, brainstem, hypothalamus, and spinal cord[53].

The blood brain barrier and blood-cerebrospinal fluid barrier are the two primary routes involved with transporting systemic IGF1 into the brain. Both barriers utilize lipoprotein receptor-related proteins along with IGF1R as transporters to enter the brain[54,55]. However, the bioavailability of IGF1 is largely determined by the amount of hormone bound to IGF binding proteins (IGFBPs). Most circulating IGF is bound by IGFBPs, which are proteins that control the distribution and functional capabilities of IGF1 throughout the body. Six different IGFBPs modulate the activity of IGFs via binding affinities exceeding that of its respective receptor and, thus, help regulate the amount of IGF1 that enters the brain[56].

**Signaling pathways**

The role of IGF1 is dependent on its binding to insulin-like peptide receptors. The three most important include the IGF1R, IR, and a hybrid receptor formed from heterodimer α-β IR and IGF1R subunits[53,57]. These receptors are important to the functional efficacy of IGF1 and have defined downstream molecular pathways. As part of the tyrosine kinase receptor family, activation of IGF1R leads to the signaling of either the mitogen-activated protein kinases-extracellular signal-related kinase (MAPK-ERK) or phosphoinositide 3-kinase (PI3K)-Akt pathways[53,57]. These pathways are involved in several important cellular processes including the regulation of gene transcription, apoptosis, oxidative stress, and cellular proliferation and differentiation.

The affinity of IGF1 varies among the three receptors with the highest affinity for IGF1R. Activation of the IGF1R is capable of directly stimulating the RAS-ERK pathway, leading to the modulation of gene transcription by way of activating ETS-like transcription factor, ELK1[57]. The capacity of insulin-like peptide receptors to initiate downstream molecular activity is modified in part by the recruitment of insulin receptor substrate (IRS) scaffolding proteins[57-59]. This scaffolding helps adjust pathway choice following receptor phosphorylation. The result is activation of PI3K-Akt and subsequent expression of downstream effectors, including glycogen synthase 3 kinase (GSK3β) and mammalian target of rapamycin[53,57,60].

**Relationship to the insulin system**

IGF1 acts primarily through binding to the IGF1R, but also shares with insulin the capacity to bind the IR and hybrid receptor[53,56,57]. Insulin is produced exclusively by β-cells of the pancreas and, hence, is strictly transported in the systemic circulation. The amount of insulin capable of entering the brain varies considerably[54,55]. Unlike IGF1, insulin appears not to be locally synthesized in adult brain cells[53,56]. Similar to IGF1, IR located on endothelial and epithelial cell membranes allow insulin to be transported into the brain from systemic circulation. IRs are concentrated mostly in the olfactory bulb, cerebral cortex, hypothalamus, hippocampus, and cerebellum[55]. The movement of systemic insulin into the brain is not controlled by binding proteins.

Both insulin and IGF1 produced in the periphery contribute to varied physiological processes. Proper peripheral IGF1 activation is necessary for insulin secretion from the pancreas and, hence, is implicated in many facets of diabetes[61]. However, their functions differ once entering the brain. IGF1R are expressed at notably higher rates in the brain than the rate IGF1 is synthesized. This differential suggests that active transport of IGF1 into the brain is required to furnish sufficient IGF1 for proper neuronal function[47-49]. For example, peripheral IGF1 supplies the brain with...
information regarding body mass, is related to neural plasticity and cognitive processes, and attenuates cognitive impairment induced by diabetes. $^{51,62,63}$ Deficiency of IGF1 can also lead to hippocampal atrophy and impaired learning. $^{64}$ Indeed, IGF1 in the brain is required for proper tissue growth in both the brain and periphery, as well as sufficient glucose regulation and insulin sensitivity. $^{65,66}$

Insulin in the periphery is well-known for its role in glucose regulation and communication with the brain to maintain energy homeostasis. Similar to IGF1, insulin is involved in modifying BBB permeability in the brain $^{35}$ with T2D patients showing greater permeability of the BBB $^{37}$. Insulin also acts on the PI3K and MAPK signaling cascades to enhance neuronal survival, plasticity, and subsequent cognitive processes $^{65,68,69}$. With that said, insulin does not necessarily regulate glucose activity in neuronal cells after entering the brain. Rather, insulin modulates energy homeostasis through its actions at the level of the hypothalamus $^{70}$.

INTEGRATING SEX HORMONES INTO DIABETES AND IGF1

Diabetes is associated with imbalances in sex steroid hormone levels. This is not surprising as androgens and estrogens are known to play an important role in body composition $^{71}$ while maintaining glucose and lipid homeostasis $^{72,73}$. Research into these imbalances suggests a complex relation between estradiol (E2) and insulin insensitivity. Several studies have reported that postmenopausal women with T2D have increased levels of circulating E2 $^{74,75}$. Elevated E2 has been correlated with the development of insulin resistance and T2D in these women $^{76,77}$. Nevertheless, there are at least two studies that have shown inconsistencies between E2 levels and the development of diabetes in postmenopausal women $^{78,79}$. There is also a link between high levels of E2 and diabetes in men. Diabetic men have shown relatively high basal levels of E2 $^{77,80}$, while men with higher levels of circulating E2 have an increased risk of developing T2D $^{81}$. Although this may simply be a product of higher body fat content as adrenal androgens are readily converted to E2 in adipose tissue $^{81-83}$, two studies reported E2 results in men were independent of obesity $^{76,80}$.

Findings with animal models suggest an opposite conclusion for E2 and diabetes, at least during reproductive ages. Male mice with streptozotocin-induced insulin insensitivity are more likely to develop diabetes than their female cohorts. This increased risk of diabetes in the males can be attenuated with E2 supplements $^{84}$. Also, mice lacking the alpha subtype of estrogen receptor (ERα) have been reported to develop insulin insensitivity $^{85}$. In contrast, these data in animals mirror those from postmenopausal women in which glucose homeostasis was positively impacted with estrogen therapy in the short term $^{86}$.

Sex differences in androgen-diabetes relations have also been reported. Postmenopausal women with diabetes displayed elevated circulating testosterone (TS) levels $^{27,75}$. Reports suggest that premenopausal women with higher levels of TS $^{76,79}$, as well as female mice administered the androgen $^{84}$, had a greater risk of developing diabetes. Another example is the link between T2D development and hyperandrogenism experienced by patients with polycystic ovarian syndrome $^{87}$. Still, much like E2, there are also studies that dispute these reports, particularly in postmenopausal women $^{77,78}$.

A clear sex difference is also indicated in that diabetic men tend to have either lower total, free, or bioavailable TS than healthy men $^{27,88,89}$. Indeed, men with the highest levels of TS were at the lowest risk and men with lowest levels of TS were at highest risk for developing T2D $^{78,79,80}$. Moreover, men undergoing androgen deprivation treatments for prostatic cancer had a greatly increased risk of developing T2D $^{91}$. Yet again, these reports are not without contradiction $^{92}$ and some studies found this relationship to be dependent on obesity $^{80,83}$.

Taken together, there are clear inconsistencies in the findings on sex hormones and diabetes. There is also an apparent lack of research focusing on sex hormones in premenopausal diabetic women that should be addressed $^{80}$. It is again important to note that many studies fail to acknowledge the possible relation of sex hormones to the IGF1 system. Findings with serum E2 data are consistent with findings from meta-analyses examining IGF1 $^{94}$, while maintaining glucose and lipid homeostasis $^{92}$, and men with lowest levels of TS were at highest risk for developing T2D $^{94,95}$. Their proposed U-shaped association of IGF1 and T2D fits into the well-defined mechanistic relationship between E2 and IGF1, described in more detail below. The relation between sex hormones and IGF1 suggests that a delicate hormonal balance is likely an important facet of diabetes-induced brain and cognitive impairment.

NEUROPROTECTION: SEX HORMONES AND IGF1

Estrogen and IGF1

An intriguing feature of neuroactive hormones is their ability to protect the CNS from damage, especially in regards to estrogen. ER activation is implicated in the maintenance of various metabolic processes that are also associated with diabetes, including glucose homeostasis and obesity $^{94,95}$. Only recently has research with animal models focused on neuroprotection from IGF1-E2 interactions. Evidence suggests that neuroprotective properties of E2 are directly related to receptor activities of insulin-like peptide receptors, mainly IGFIR. E2 and IGF1 work in tandem to reciprocally modulate and facilitate ER and IGFIR activation of the PI3K-Akt and MAPK-ERK signaling cascades $^{96-100}$. IGF1 shows differential sensitivities to the two
estrogen receptor subtypes with ERα being more sensitive than ERβ[97,101]. Selective inhibition of IGF1R, for instance, downregulates ERα expression in the hypothalamus, hippocampus, and cerebral cortex, with the only significant changes of ERβ occurring in the cerebellum[38]. Many glial and neuronal cells in the brain express IGF1R and both ER subtypes[102]. In particular, ERα is uniquely capable of increasing IGF1R activity of downstream PI3K-Akt signaling in rodent models[103,104]. ERα activation also increases the binding of p85 and IRS-1 regulatory subunits of PI3K and, thus, may be one mechanism assisting in Akt pro-survival signaling through the IGF1R[96,97] (Figure 1).

Administration of E2 to mice increased IGF1R and ERα activity in the brain, enabling activation of IGF1R and downstream PI3K-Akt pathway signaling[97]. Similarly, IGF1 and insulin modulated ER effects on gene transcription and the PI3K-Akt-GSK3β signaling cascade[38,98,103,105,106]. GSK3β is a protein kinase known particularly well for its role in glycolgen synthesis. However, as reviewed by Jacobs et al[100], recent attention has turned to the dual pro- and anti-apoptosis capabilities of GSK3β regulated through multiple different pathways. Indeed, the neuroprotective effects of IGF1 may be consequent to Akt-derived inhibition of GSK3β in a hypoxic state[107] (Figure 1).

Activation of the MAPK pathway is another important signal transduction pathway involved with regulating gene transcription and cellular proliferation and differentiation, particularly in cancer[108]. However, multiple studies have demonstrated that the neuroprotective properties of estrogen are also derived from its ability to regulate MAPK signaling in the brain[38]. Both estrogen and IGF1 can facilitate MAPK signaling through the IGF1R, with IGF1 increasing ERα activities in the presence of E2[104]. Akt inhibitors are capable of nullifying the neuroprotective effects of IGF1 and E2 regardless of MAPK signaling[99,104], while ERK suppression increases PI3K-Akt activity via ER and IGF1R heterodimers[39]. Thus, it appears the PI3K-Akt pro-survival signaling cascade is the most involved with the neuroprotective coupling of E2 and IGF1[39].

It is important to note that IGF1 and E2 have a remarkable reciprocity. Inhibition of ER activity can downregulate IGF1R expression in the hippocampus[109], a brain region known to atrophy in patients with diabetes and glucose intolerance[110-112]. Similarly, IGF1 has the capacity to upregulate ERs in the hippocampus and is impaired following administration of IGF1R antagonists[109]. Agonists or antagonists of either hormone can respectively facilitate or inhibit the neuroprotective and memory enhancing properties of the other[96,109,113-115]. This has led some to suggest that cooperation between IGF1R and ER is required for many E2-induced neuroprotective processes. The present section does not, however, do justice to the complexity of the relation between estrogen and IGF1 receptors. A fuller explanation can be found in one of several reviews[37-39,104,109,117].

### Androgens and IGF1
Far less research has examined a functional link between IGF1 and androgens in the brain. This is an unfortunate but common trend in neuroendocrinology. Estrogens are the most intensely studied gonadal hormone, despite estrogens and androgens sharing metabolic pathways and functional properties. Much of the current literature on IGF1-androgen relations are directed at the periphery, particularly prostate cancer and motor systems, for which there are a number of recent reviews[118,119]. Few studies have examined IGF1-androgen interactions in neuroprotection[120,121] and none, to our knowledge, have empirically examined this interaction in diabetes. Therefore, we have relied on peripheral data, often from in vitro experiments, to extrapolate the androgen receptor (AR) brain discussion.

There is evidence that the two main androgens, TS and dihydrotestosterone (DHT), are capable of neuroprotection through binding the AR[122-126]. Similar to ERα, androgen activation of the AR in mouse vas deferens epithelial cells can modulate the p85 regulatory subunits of PI3K and subsequently trigger Akt expression (Figure 1). Inhibiting the AR prevents these signaling effects[127]. Phosphorylation of MAPK and Akt can also increase AR activation in low androgen and estrogen concentrations, as well as increase the neuroprotective activities of ERα and AR[128]. Recent findings showed that DHT, which has a higher affinity than TS for the AR, prevents apoptosis in a C6 glial cell line through the PI3K-Akt signaling cascade[126]. These effects were also impaired by inhibition of PI3K and suggest a functional relationship between apoptosis and AR activities.

Interestingly, studies have demonstrated that binding of DHT to the transmembrane AR impairs MAPK and PI3K signaling and subsequent neuroprotection from DHT or E2[129-132]. This suggests that nuclear activation of the AR by DHT is likely one mechanism behind DHT’s neuroprotective properties[130]. DHT may also interact with effectors downstream of ER and IGF1R signaling. Both TS and DHT can activate the MAPK-ERK signaling cascade[132] which has been shown to induce ribosomal S6 kinase (Rsk) expression. Rsk signaling can lead to the inhibition of the pro-apoptosis Bad protein and the activation of downstream effectors including the ER, GSK3β and ELK1[133] (Figure 1).

One possible explanation for the neuroprotective role of androgens is the conversion in the steroid metabolic cascade of TS into E2 by the enzyme aromatase. That is, TS may be involved in neuroprotection only to the extent that TS is a precursor for E2, which is capable of activating MAPK or PI3K signaling through the ER and IGF1R. The aromatization of TS into E2, as well as the aromatase enzyme, have been suggested to play an important role in neuroprotection[134-139].

The ratio of endogenous TS to E2, and subsequent influences of aromatized TS, is indeed a topic of recent interest[26]. Increased local synthesis of E2 from elevated aromatase expression is seen in models...
of neuroprotection from other brain disorders, e.g., stroke. More pertinent to this review, streptozotocin-induced diabetes causes a considerable reduction in aromatase synthesis in female and male reproductive systems. Notably, inhibition of aromatase decreases E2 and impairs insulin sensitivity and peripheral glucose disposal in healthy males, although the influence this may have on brain integrity and cognitive outcomes remains debated. Few in vivo studies examining these sex steroid metabolites have focused on MAPK or PI3K signal cascades in the brain. There is, however, evidence that 3α-Diol inhibits protein kinase A expression in the rat hippocampus. Others have reported that streptozotocin-induced diabetic mice had lower levels of TS and 3α-Diol in the cerebral cortex, and lower levels of DHT and 3α-Diol in the spinal cord. It is still unclear, though, whether 3α-Diol and 3β-Diol interact with or initiate the MAPK or PI3K signaling cascades following activation of the ER, AR, or, possibly, IGF1R. None of these explanations clarify fully the ability of the AR to directly trigger these signaling cascades. We do not aim to discount the neuroprotective mechanisms of ER and AR, or the clear link between E2 and IGF1 processes in neuroprotection. Rather, we simply suggest that androgen-derived neuroprotection may be intertwined with IGF1, the activation of insulin-like peptide receptors, and/or the IGF1R and ER coupling. Given the common signaling pathways between these hormones, we suggest future research should aim to include androgens and AR activities into the ER-IGF1R neuroprotective coupling, as well as serum comparisons in brain-health outcomes of diabetic patients.

CONCLUSION
The reciprocity of IGF1 and estrogen in neuroprotective processes is well-established in cell cultures and...
animal models. Interactions between androgens and IGF1 may also play an important role in the E2-IGF1 neuroprotective coupling. Both estrogens and androgens enact their neuroprotection through similar, but not identical, signal transduction pathways. Recognition of this has led us to consider the possibility that these sex hormones may work together with IGF1 and insulin-like peptide receptors to modulate MAPK and PI3K signalling and their neuroprotective properties.

Regulation of MAPK and PI3K activity may also be a driving force behind the structural changes, atrophy of brain regions, or functional changes, often observed in diabetic patients. Drawing conclusions from imaging data in humans to those found in animal models is indeed difficult. Nevertheless, there is a need for a clearer mechanistic explanation grounding the cognitive decline and brain abnormalities observed in diabetic patients.

Future studies in human research on diabetic brain integrity should integrate hormone titre measures to help substantiate sex differences in brain-health outcomes of diabetic patients. This approach may also assist in identifying region-specific brain abnormalities resulting from fluctuations in IGF1 and sex hormones between men and women. Moreover, animal models examining the E2-IGF1 coupling in neuroprotection should employ streptozotocin-induced diabetes, as well as the possible role of androgens and AR activities. These conclusions warrant further examination of the variability present in cognitive and brain-health outcomes for patients with diabetes as a result of sex hormone relations to IGF1, insulin, and the insulin-like peptide receptors.

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