Review Article

The Insulin-like Growth Factor System: Towards Clinical Applications

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Abstract

Insulin-like growth factors (IGF-I and –II) are important endocrine, paracrine and autocrine mediators of physiological growth. They promote cellular proliferation, survival and differentiation. Their effects are mediated mainly through the IGF-I receptor, but IGFs also bind to the IGF-II/mannose 6-phosphate and insulin receptors. IGF activity is modulated by a family of six high-affinity IGF binding proteins (IGFBPs); in most situations, IGFBPs inhibit IGF actions but they may also enhance them. Assays are now available for IGF-I, IGF-II and individual IGFBPs. IGF-I and IGFBP-3 assays have some utility in the diagnosis and management of acromegaly and growth hormone deficiency. There is a large body of in vitro and in vivo evidence supporting a pathogenic role for alterations in the IGF system in many diseases, including diabetes, cancer, cardiovascular disease and neuromuscular disease. More recently, epidemiological studies have linked high IGF-I levels with some cancers and low IGF-I levels with ischaemic heart disease. Preliminary studies of recombinant IGF-I as a treatment for diabetes, osteoporosis and neuromuscular disease have been performed in humans. In contrast, there is considerable interest in developing IGF inhibitors for the treatment of cancer. This apparent paradox highlights the need to develop therapeutics beyond the natural ligands and inhibitors, with characteristics such as ligand and tissue specificity. This will only become possible as we increase our understanding of this complex system. Additionally, as IGF and IGFBP assays are becoming more readily available, their role in the diagnosis and monitoring of diseases should be more clearly defined in the near future.

The IGF System (Table 1)

IGFs are central mediators of physiological growth.[1-3] Dysregulation of the IGF system has been implicated in many diseases, notably cancer.[3-7] Most of the effects of IGFs are mediated by the IGF-I receptor but IGFs also bind to the insulin and IGF-II/mannose 6-phosphate receptors. Additionally, IGF actions are modulated by a family of high affinity IGF binding proteins (IGFBPs), which may either inhibit or potentiate IGF actions.[7-9] There is substantial interest in both the basic science and potential clinical applications of the IGF system because of its important roles in normal physiology and the pathogenesis of many common diseases. The availability of new assays and assay platforms for IGFs and IGFBPs has the potential to lead to their more widespread use in clinical research and patient management. This brief review highlights our current state of knowledge of the IGF system. Many of the references are more detailed, specific reviews that may be of interest to some readers.

IGFs

IGF-I and IGF-II are ~7.5 kDa peptides with 67% amino acid identity.[10] They are also highly homologous with insulin with respect to sequence and structure.[11] IGF-I, -II and insulin are believed to derive from a common ancestral gene. However, whereas insulin is primarily a metabolic hormone, IGFs promote proliferation, survival, and/or differentiation of most cell types. Nevertheless, IGFs retain insulin-like metabolic activity and IGF-I has ~8% of the potency of insulin on a molar basis.[12] IGFs are synthesised by most organs and may act as endocrine, paracrine and/or autocrine growth factors.

In most organs, IGF-I synthesis is regulated by growth hormone (GH).[10,11] In particular, most circulating IGF-I

Table 1. The Insulin-like Growth Factor System.

Ligands
IGF-I
IGF-II
Receptors
IGF-I
IGF-II/mannose 6-phosphate
Insulin, including insulin receptor isoform A
IGF binding proteins
IGFBP-1
IGFBP-2
IGFBP-3
IGFBP-4
IGFBP-5
IGFBP-6

derives from the liver under GH control. Circulating IGF-I levels fluctuate throughout life, being relatively low in childhood, peaking at puberty and then slowly declining through adult life.

Other factors important in IGF-I regulation include nutritional status, sex steroids and insulin. Circulating IGF-I levels may be low in conditions including critical illness, poorly controlled diabetes, malnutrition, cirrhosis and hypothyroidism.[10,13]

IGF-II expression is not regulated by GH or nutritional status to any great extent. In rodents, IGF-II levels are high prenatally and expression ceases in most organs soon after birth. In contrast, circulating IGF-II levels in man are about 4 times higher than those of IGF-I and they do not fluctuate greatly with age.

IGF Receptors

The IGF-I receptor consists of two disulphide-linked αβ heterodimers and it is structurally similar to the insulin receptor.[3,11] Both IGF-I and IGF-II bind the IGF-I receptor with high affinity and insulin binds with lower affinity. Most of the actions of IGF-I and –II are mediated by this receptor. Upon ligand binding, the receptor has tyrosine kinase activity resulting in autophosphorylation, recruitment of docking proteins such as IRS-1 (insulin receptor substrate-1) and subsequent stimulation of many signal transduction pathways, including Ras/MAP (mitogen-activated protein) kinase, PI3 kinase/PKB (protein kinase B) Akt and PI3 kinase/mTOR (mammalian target of rapamycin)/S6K.[3] Activation of these pathways results in cell proliferation, survival, and increased protein translation.

The IGF-II/mannose 6-phosphate (M6P) receptor is structurally distinct from IGF-I and insulin receptors.[14] It binds IGF-II with high affinity, IGF-I with far lower affinity and does not bind insulin. As its name implies, it also binds M6P-containing glycoproteins, which subserves its role in sorting lysosomal enzymes. The IGF-II/M6P receptor has a short intracytoplasmic domain. The extent to which this receptor mediates IGF-II actions is unclear; its major IGF-related role appears to be IGF-II internalisation and clearance. The IGF-II/M6P receptor also binds a number of other ligands, including latent transforming growth factor β (TGFβ), retinoic acid and the urokinase plasminogen activator receptor. A soluble form of this receptor which lacks the transmembrane and intracellular domains is found in the circulation.

IGFs also bind to the insulin receptor, which mediates some of their metabolic effects.[10] Recently, it has been shown that IGF-II but not IGF-I binds to the insulin receptor isoform A, which is overexpressed in some cancers; this receptor also mediates some of the proliferative effects of IGF-II.[15]

IGFBPs

IGF actions are modulated by a family of six structurally-related binding proteins (IGFBPs 1-6), which bind IGFs but not insulin with high affinity.[8,9,16] Within the circulation, IGF-I and –II are found in nanomolar concentrations, compared to picomolar concentrations of insulin. The net circulating IGF activity is therefore more than sufficient to cause profound hypoglycaemia. This is prevented by binding of more than 99% of IGFs to IGFBPs.[16] In particular, IGFBP-3 is the predominant circulating IGFBP. IGFBP-3 and IGF-I or –II form a 150 kDa ternary complex with an 85 kDa acid-labile subunit (ALS) in the circulation; this carries ~75% of circulating IGFs. The half-life of IGFs is dramatically increased within ternary complexes as they cannot leave the circulation. IGFBP-5, but not the other IGFBPs, is also found in ternary complexes.[9] The ternary complex is believed to form an IGF reservoir.

About 25% of circulating IGFs are bound to other IGFBPs in binary complexes.[16] Of these, IGFBP-1 is metabolically regulated and its expression is inhibited by insulin. Binary complexes, sized ~40 kDa, can leave the circulation. IGFBPs may serve to target IGFs to specific tissues.

IGFBPs are ubiquitously expressed and may have important autocrine or paracrine roles.[8] In most situations, IGFBPs inhibit IGF actions, since they bind IGFs with higher affinity

than the IGF-I receptor. In some circumstances, however, some IGFBPs, especially IGFBP-3 and –5, may potentiate IGF actions. The mechanism of potentiation is incompletely understood but may involve cell-association and subsequent release of IGFs in an optimal manner for binding to the IGF-I receptor.

In the last few years, it has become apparent that some IGFBPs, especially IGFBP-3, have IGF-independent effects.[9] IGFBP-3 may bind to specific cellular receptors and is also imported into the nucleus of some cells, where it may interact with transcription factors such as the retinoid X receptor α.[17] IGFBP-3 inhibits proliferation and promotes apoptosis of some cells in an IGF-independent manner.

IGF/IGFBP Assays

IGF-I

Immunoassays for IGF-I were first developed over 20 years ago. A major potential problem with these assays is interference by IGFBPs.[18,19] The earliest assays used a non-equilibrium method to overcome this problem but it did not prove to be a reliable approach. Other approaches have been used subsequently: (i) removal of IGFBPs (ii) saturation of IGFBPs (iii) use of an IGF analog with low IGFBP affinity as a tracer.

The 'gold standard' for removal of IGFBPs from biological samples prior to IGF-I analysis is acid gel chromatography. However, this is time-consuming and expensive and not practical for routine use. A number of quicker methods have been developed; of these, acid-ethanol extraction is used most commonly. However, in some situations, IGFBP removal is incomplete using this method. Another approach is to add an excess of IGF-II to extracted samples that will saturate IGFBPs and allow release of all IGF-I for subsequent assay. This requires the use of anti-IGF-I antibodies with very little, if any, cross-reactivity with IGF-II, but these are now readily available; a major consideration is the expense of IGF-II. The third approach uses an IGF-I analog, such as des(1-3)IGF-I, which has lower affinity for IGFBPs, as tracer. This analog binds IGFBP-3, the most abundant IGFBP in the circulation, with ~10-fold lower affinity than IGF-I, and other IGFBPs with far lower affinity, thereby minimising interference.

'Free' IGF-I Assays

Less than 1% of circulating IGF-I is found in the free form as most is bound to IGFBPs in ternary or binary complexes. IGF-I in ternary complexes of IGFBP-3/5 and ALS leaves the circulation very slowly, whereas free and IGFBP-bound IGF-I have much shorter half-lives. Some authors hold the view that it is preferable to measure free IGF-I because it is the biologically active form.

There are two types of free IGF-I assay.[20] One is an equilibrium assay that relies on separation of free from bound IGF-I using ultrafiltration across a molecular weight cut-off membrane. The other is a direct non-equilibrium immunoradiometric assay that relies on an antibody binding free but not bound IGF-I. Results from the two assays do not always concur. The role of these assays in clinical medicine and epidemiological studies is not completely defined.

IGF-II Assays

Immunoassays are available for IGF-II. The potential for IGFBP interference is the same as that noted above for IGF-I and samples must be treated to minimize this interference. The ultrafiltration assay for free IGF-I can also be used for IGF-II.

IGFBP Assays

Immunoassays are now available for IGFBPs 1-6.[16] In contrast to IGF assays, in which IGFBPs interfere considerably, the presence of IGFs does not interfere with almost all IGFBP assays. IGFBP-3 is the predominant circulating IGFBP and is probably the most commonly measured. It is GH-dependent and it has been suggested that measurement of IGFBP-3 may be helpful in the diagnosis of acromegaly and GH-deficiency.

Acid Labile Subunit (ALS) Assays

ALS binds to complexes of IGFs with IGFBP-3 or IGFBP-5 to form the 150 kDa circulating ternary complex, which accounts for ~75% of circulating IGFs.[21,22] ALS is synthesized in the liver and is GH-dependent.[23] It is present in molar excess to IGFBP-3 in serum and therefore ~60% is unbound.[23,24] ALS immunoassays have been developed[24, 25] but have not yet received widespread clinical use.

IGFs and Clinical Medicine (Table 2)

Acromegaly/Growth Hormone (GH) Deficiency

Acromegaly is usually caused by a GH-secreting pituitary tumour. Excessive GH secretion results in increased circulating IGF-I levels. Since IGF-I levels remain relatively constant throughout the day and GH secretion is episodic, measurement of IGF-I is one of the preferred methods for diagnosing acromegaly and following its activity after treatment. However, IGF-I levels need to be compared to an age-adjusted normal range since they decline with age.[26]

Table 2. Diseases in which the IGF system is implicated.

Acromegaly
Growth hormone deficiency
Cancer
Atherosclerosis
Diabetes
Osteoporosis
Neuromuscular disorders

In GH-deficient children, IGF-I levels are usually low although the correlation between provocative GH tests and IGF-I levels is imperfect.[27] This may be due to overlap between normal and low IGF-I levels in children aged less than 5 years, and also to variability in GH responses to provocative stimuli. Once again, comparison of IGF-I levels with an age-adjusted normal range is essential. It has been suggested that measurement of IGFBP-3 may also be useful for the diagnosis of GH-deficiency, although the correlation with provocative tests is also imperfect.[27] Some studies have shown that measuring both IGFBP-3 and IGF-I levels does not improve the accuracy of the diagnosis of GH-deficiency over measuring IGF-I levels alone.[28]

Cancer

Basic

Several thousand studies of the IGF system in cancer have been published, ranging from studies of basic in vitro biology to epidemiology to clinical intervention. IGF-II is over-expressed in and has been implicated as an autocrine growth factor for many tumours.[29] These include paediatric tumours including Wilms' tumour, rhabdomyosarcoma and neuroblastoma, as well as adult tumours including hepatoma and colon cancer.[29] IGF-II may be over-expressed by a number of mechanisms, including loss of genomic imprinting and increased transcription due to loss of repressor function or changes in promoter sites.[7] It was recently suggested that loss of IGF-II imprinting may be the basis of a useful DNA-based predictive blood test for colorectal cancer risk.[5]

In many in vitro systems, the IGF-I receptor is critical for tumorigenesis.[30] Cellular processes mediated by this receptor include proliferation, survival and transformation (defined as the ability for cells to grow in soft agar and form tumours in nude mice). Inhibition of the IGF-I receptor using antisense or antibodies inhibits in vitro and in vivo growth of many tumours.[7]

The *M6P/IGF2R* may be a tumour suppressor gene due to the role of the IGF-II/Man 6-P receptor in clearing IGF-II, regulating lysosomal enzyme targetting and activating the growth inhibitor TGF-β.[14] Loss of heterozygosity together with mutation of the other allele, resulting in loss of IGF-II/Man 6-phosphate receptor expression, is frequently found in many cancers.

The role of circulating IGF-I in tumorigenesis has been recently studied in animal models. Colon cancer growth and metastasis is reduced in mice with decreased circulating IGF-I levels due to liver-specific IGF-I gene deletion.[31] Onset and growth of chemically and genetically-induced breast cancer is also delayed in these mice.[32]

Epidemiology

Patients with long-standing, active acromegaly, who have chronically elevated IGF-I levels, are at increased risk of colonic polyps and neoplasia.[33] Breast and prostate cancer may also be increased although further studies are needed. In contrast, there is no evidence of increased cancer risk following GH replacement therapy in children with short stature.[34]

Over the last 5-6 years, a growing number of papers have described associations between serum IGF-I levels and increased risk of a range of cancers, including prostate, breast, colon and lung.[7] The first prospective study showed that men with plasma IGF-I levels in the highest quartile had a relative risk of 4.3 (95% confidence interval 1.8-10.6) for the development of prostate carcinoma over 7 years compared with men in the lowest quartile.[35] A meta-analysis of a small number of studies confirmed that men with IGF-I levels in the upper quartile had an ~2-fold higher risk of developing prostate cancer.[36] Some studies have not found this association and offered the alternative explanation that IGF-I may be a marker of pre-clinical tumours.[37] It remains controversial whether the association between IGF-I levels and prostate carcinoma is independent of prostate specific antigen levels.[35,38]

In females from the Nurses' Health Study, pre-menopausal women aged less than 50 with plasma IGF-I levels in the highest tertile had a relative risk of 4.58 (95% confidence interval 1.75-12.0) for the development of breast carcinoma over 28 months compared with women in the lowest tertile.[39] There was no relationship between plasma IGF-I levels and breast cancer risk in post-menopausal women in that study, but some other studies have found such a relationship.[40] It should

be noted that not all studies have shown this relationship between IGF-I levels and breast cancer risk.[7]

A prospective case-control study also found a ~2.5-fold (95% confidence interval 1.15-5.46) increased risk of colorectal cancer in men with IGF-I levels in the highest quintile compared with those in the lowest.[41] Similar findings have been observed in some, but not all subsequent studies.[7,42,43] Increased IGF-II levels have also been implicated as a marker[44] or predictor[45] of colon cancer.

In many studies, circulating IGFBP-3 levels are inversely related to cancer risk, although this association did not reach statistical significance in some studies and was not observed in others.[7] IGFBP-3 inhibits the proliferative and antiapoptotic actions of IGFs in many circumstances. IGFBP-3 is also antiproliferative and proapoptotic for many tumour cells independently of its effects on IGFs. This has led to the notion that patients with high IGF-I and low IGFBP-3 may be at highest risk for the subsequent development of cancer. Some investigators therefore advocate titrating GH replacement doses in GH-deficient patients according to both IGF-I and IGFBP-3 levels.[34]

In contrast to IGFBP-3 levels, there is some evidence that serum IGFBP-2 levels are elevated in patients with many cancers, including prostate, lung, colon and ovarian cancer.[46] IGFBP-2 levels are often correlated with increased malignancy and in vitro data suggest that IGFBP-2 increases tumorogenicity of some cancer cells.

The antiapoptotic effect of IGF-I may be particularly relevant to the possible predisposition to cancer in patients with elevated circulating IGF-I levels. Normally, death of genetically damaged cells might occur due to apoptosis, but high IGF-I levels may prevent this, resulting in tumour formation from these cells.

Irrespective of the mechanisms involved in the relationships between circulating IGF-I and IGFBP levels and cancer risk, these measurements may become a useful part of malignancy screening in the future. This will be especially true if IGF-specific therapeutics become available for the prevention or treatment of these cancers.

Non-islet Cell Tumour Hypoglycaemia (NICTH)

NICTH is a rare condition that provides considerable insight into the metabolic potential of the circulating IGF system.[47] In this condition, the tumour, which is usually a large mesenchymal sarcoma, synthesizes and secretes large amounts of a partially processed IGF-II precursor. Despite normal binding of this precursor to IGFBPs, formation of the 150 kDa ternary complex is impaired. This results in excess levels of the IGF-II precursor leaving the circulation. Since the IGF-II precursor binds to IGF receptors and has normal or increased biological potency, severe, refractory hypoglycaemia may result. GH secretion is markedly suppressed due to feedback inhibition by the IGF-II precursor, resulting in decreased IGF-I, IGFBP-3 and ALS levels.

Cardiovascular Disease

Basic

IGF receptors and IGFBPs are expressed in the heart and levels change regionally following infarction.[48,49] Further, IGF-I stimulates cardiomyocyte hypertrophy and contractility in rats with heart failure.[50] GH and IGF-I may also improve cardiac performance by decreasing peripheral vascular resistance.[51]

The IGF system is also present in blood vessels and IGF-I increases proliferation of vascular smooth muscle cells.[52] A recent paper suggests that IGF-II is central to the development of atherosclerosis in a genetic mouse model.[53]

Epidemiology

Patients with GH deficiency and low IGF-I levels have increased mortality due to cardiovascular disease.[54] However, excess GH in acromegaly is also associated with increased cardiovascular risk due to cardiomyopathy.[54] Treatment of both these conditions ameliorates the cardiovascular risk.

A prospective nested case-control study showed that subjects with a serum IGF-I in the lowest quartile had a 1.94-fold (95% confidence interval 1.03-3.66) higher risk of developing ischaemic heart disease over 15 years than subjects with IGF-I levels in the highest quartile.[55] Low levels of IGFBP-3 were protective and a population with both low IGF-I and high IGFBP-3 levels had a ~4.1-fold (95% confidence interval 1.5-11.2) higher risk than the index population. These risks persisted after correction for known cardiac risk factors.

Therapeutic

In 1996, a small uncontrolled study suggested that three months of GH administration improved the cardiac function and clinical status of patients with dilated cardiomyopathy.[56] Since then, a number of further studies have been performed giving GH to patients with heart failure for up to six months with variable results in terms of clinical benefit.[54] Further

studies are needed to determine which patient groups may benefit from this treatment and the optimal doses and duration of GH treatment for these patients.

Diabetes

The Pancreatic IGF System and the Development of Diabetes

In recent years, a very interesting literature on the role of the IGF system in pancreatic β-cell development and function has evolved. IGF-II expression is decreased in β-cells during the wave of apoptosis that occurs post-natally, suggesting that IGF-II acts as a survival factor.[57] Mice with β-cells lacking the IGF-I receptor have impaired glucose tolerance and insulin secretion,[58] and overexpression of IGF-I in β-cells leads to recovery from experimental type 1 diabetes.[59]

Epidemiology

Non-diabetic adults with serum IGF-I levels above the median had a relative risk of 0.50 (95% confidence interval 0.26-0.95) of developing glucose intolerance compared with adults whose levels are below the median.[60] In the same study, two-hour glucose levels during a glucose tolerance test were lower in subjects with both high IGF-I levels and low IGFBP-1 levels. This was not seen in subjects with both high IGF-I and IGFBP-1 levels, suggesting that the interaction between IGFBP-1 and IGF-I may be important for glucose homeostasis. A Dutch study showed that non-carriers of a 192 bp polymorphism in the IGF-I gene promoter had lower circulating IGF-I levels and a 1.7-fold (95% confidence interval 1.1-2.7) higher risk of developing type 2 diabetes than subjects with this allele; they also had a 1.7-fold (95% confidence interval 1.1-2.5) higher risk of myocardial infarction.[61] However, a study in the UK was unable to confirm these findings.[62]

Serum IGFBP-1 levels are inversely related to risk of impaired glucose tolerance as well as triglycerides, body mass index, fasting insulin levels and blood pressure; it appears to be a marker of hepatic insulin resistance.[63] Inverse correlations of IGFBP-1 with blood pressure, body mass index, and insulin levels as well as a positive correlation with HDL levels was also seen in subjects with type 2 diabetes.[64]

IGF levels in diabetes

Circulating IGF-I and IGFBP-3 levels are decreased in poorly-controlled diabetic patients and in diabetic rat models.[10] GH levels are increased in diabetic patients, so that GH resistance underlies the decrease in IGF-I levels. Levels of IGFBP-1, expression of which is inhibited by insulin, are increased in insulin-dependent diabetes.

Not all studies have shown decreased IGF-I levels in type 1 diabetic patients. The discrepancies between studies may in part relate to differences in assay technologies, since it has recently been suggested that methods using excess IGF-II to displace IGF-I from residual IGFBPs that may otherwise interfere with immunoassays may allow more accurate IGF-I measurement in diabetic subjects.[19]

Therapeutic

Many of the hypoglycaemic effects of IGF-I are mediated by the IGF-I receptor rather than the insulin receptor.[10, 65] It was therefore thought that IGF-I might 'bypass' the insulin resistance of non-insulin-dependent diabetic patients. Short-term studies and some long-term studies confirmed the efficacy of IGF-I treatment.[66] Low-dose IGF-I has also been used to supplement insulin therapy in diabetic patients.[67] As well as having intrinsic hypoglycaemic properties, IGF-I increases insulin sensitivity directly and also indirectly by decreasing levels of GH.

IGF-I has a number of dose-limiting side effects, including oedema, jaw pain, headaches, Bell's palsy and hypoglycaemia. For this reason, an IGF-I/IGFBP-3 complex has been used; this complex reduces insulin requirements in patients with type 1 diabetes with minimal side effects in a short-term study.[68]

There are a number of further considerations with regard to IGF-I treatment for diabetes. There is considerable interest in the possible role of IGFs in the development of diabetic complications.[8,10,69] Regulatory agencies have been particularly interested in the possibility of IGF-I treatment accelerating diabetic retinopathy. There is also concern about the potential relationship between IGF-I levels and the development of cancer as described above. These issues will need to be resolved satisfactorily before IGF-I becomes a viable treatment option for diabetes.

Osteoporosis

Basic

The IGF system plays a crucial role in skeletal development.[70] At the cellular level, IGFs regulate differentiative functions of osteoblasts and osteoclasts. Knockout mice with targeted deletion of the IGF-I or IGF-I receptor genes have low bone mineral density and/or short bones, and IGF-I is thought to be important for bone mineralization.

Epidemiology

A cross-sectional study showed a relationship between circulating IGF-I levels and femoral or lumbar bone mineral density in elderly women,[71] although other studies have not found this association in other cohorts. Post-menopausal women with serum IGF-I levels below the median had a 3.1-fold increased risk of osteoporotic fracture (95% confidence interval 1.5-6.4) than those with IGF-I levels above the median; this risk remained 2.8-fold (95% confidence interval 1.3-6.0) after correction for bone mineral density and lean body mass.[72] No relationship between fractures with IGFBP-3 levels was found in this study.

Therapeutic

Since IGF-I stimulates mineralization and levels decline with age, IGF-I has been proposed as a treatment for osteoporosis. However, one year of low-dose IGF-I treatment did not alter bone density in healthy post-menopausal women.[73] Another study showed that low-dose IGF-I increased bone density in osteopenic patients with anorexia nervosa.[74] The role of IGF-I treatment in osteoporosis clearly requires further study.

Muscle

IGFs are potent stimulators of myoblast proliferation and differentiation and they promote muscle hypertrophy.[75] There is considerable interest in the possibility of IGF-I being used as a treatment in a range of muscular conditions including age-related wasting and muscular dystrophy. In animal models, IGF-I has proved to be effective in stimulating muscle hypertrophy and function, whether delivered systemically or locally via gene transfer or transgenic overexpression.[75-78]

Motor neurone disease is a progressive, lethal neuromuscular disease involving motor neurone degeneration. Adenoviral delivery of IGF-I has recently been shown to delay progression and prolong survival in a mouse model of this disease.[79] Human studies of IGF-I treatment in this disease have shown marginal effects in delaying progression, which may relate to limited delivery to the spinal cord following systemic administration.

Critical Illness

Circulating IGF-I levels are low in critical illness, and this is thought to be due to GH resistance acutely. For this reason, it was postulated that administration of high doses of GH may be useful in critically ill patients to attenuate catabolic effects of the illness. However, two prospective, double-blind, randomised studies clearly showed that morbidity and mortality were increased in critically ill patients receiving high doses of GH.[80] Circulating IGF-I levels were markedly increased by GH; it is unlikely that this is relevant to the observed outcome, but the precise mechanisms remain unclear.

In patients with prolonged critical illness, pulsatile secretion of anterior pituitary hormones, including GH, is reduced and wasting is a severe problem. Studies of treatment using anterior pituitary secretagogues to restore normal pulsatility are underway.

Conclusions

The IGF system is undoubtedly important both in normal physiology and in the pathophysiology of many diseases. The challenges for the future are to increase our basic understanding of this complex system so that IGF-based therapies can be developed for these diseases without interfering with physiological processes. The apparent paradox, whereby some diseases are associated with excess IGF activity and others are associated with IGF deficiency, highlights the need to develop therapeutics beyond the natural ligands and inhibitors. Optimally, these should have characteristics such as ligand and tissue specificity. Additionally, as IGF and IGFBP assays in humans are becoming more readily available, the role of their measurement in the diagnosis and monitoring of diseases should also be more clearly defined in the near future.

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