Insulin-like growth factor I in essential hypertension

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CASE PRESENTATIONS

Patient 1. A 42-year-old white man was referred to the University Clinic of the University of Navarra for evaluation of arterial hypertension. Three years earlier, the patient had been told he had elevated blood pressure during an insurance medical examination. No antihypertensive therapy was prescribed during the intervening period.

His father had had hypertension and had died of a noncardiovascular cause at age 70. The patient had had two episodes of urinary tract infection, but a rapid-sequence pyelogram did not reveal any abnormalities. He suffered often from headaches, but he had no palpitations, sweating, or orthostatic falls in blood pressure. He had no additional cardiovascular risk factors: he had never smoked; glucose tolerance was normal; and plasma cholesterol concentration was below 6.35 mmol/liter.

On presentation at the outpatient clinic, his blood pressure was 168/110 mm Hg, and the pulse rate was 74 beats/min and regular. The body mass index was 24 kg/m². Physical examination showed evidence of an enlarged left ventricle and a grade 2/6 mid-systolic ejection murmur. No carotid or abdominal bruits were heard. Pulses in the extremities were normal. No edema was present. Neurologic examination was normal. Funduscopic examination revealed mild arteriolar narrowing and arteriovenous crossing changes.

Laboratory evaluation revealed: fasting plasma glucose, 5.0 mmol/liter; serum cholesterol, 5.95 mmol/liter; serum triglycerides, 1.40 mmol/liter; serum potassium, 4 mmol/liter; serum creatinine, 95 μmol/liter (1.1 mg/dl); creatinine clearance, 112 ml/min/1.73 m² body surface; and 24-hour urine albumin excretion, 245 mg. Urinalysis revealed no other abnormalities. An electrocardiogram showed a Sokolow-Lyon voltage of 3.9 mV. Doppler ultrasonographic examination of the heart disclosed increased left-ventricular mass index (LVMI = 141 g/m²) and increased left-ventricular relative wall thickness (RWT = 0.47); parameters of diastolic and systolic function were within normal limits. Renal ultrasonography revealed normal-sized kidneys with no parenchymal abnormality. No other medical problems were identified.

The patient was asked to seek dietary counseling to reduce his sodium chloride intake, and lisinopril (10 mg once daily) was prescribed. Over the next three months, his blood pressure remained about 150/100 mm Hg, and the urinary sodium excretion ranged between 80 and 100 mmol/day. The lisinopril dose was increased to 20 mg daily. Under this therapeutic regimen, blood pressure fell to below 140/90 mm Hg during the next nine months. One year after the initial medical examination, a cardiac echocardiogram revealed diminution of the left-ventricular mass index (133 g/m²) and the RWT (0.43), and nephelometric analysis of the urine revealed a 24-hour albumin excretion of 80 mg.

Patient 2. A 52-year-old white woman was referred to the University Clinic of the University of Navarra for the evaluation of recent-onset hypertension. She had been normotensive one year earlier. She had a strong family history of cardiovascular disease: Her father died at age 55 with hypertension and a myocardial infarction, and her mother died at age 60 of hypertension and a cerebrovascular accident. The patient did not smoke and drank alcohol only occasionally.

The patient described herself as a healthy, active individual without medical complaints. She had never used oral contraceptives or cardiovascular drugs. Hypercholesterolemia had been detected during a routine medical examination; only dietary treatment had been recommended.

Physical examination revealed a thin, well-developed, well-nourished female. The body mass index was 26 kg/m². The blood pressure was 159/100 mm Hg. Cardiac examination disclosed a normal PMI, and normal sounds were noted. The abdomen was not remarkable; no abdominal bruit was audible. No edema was evident in the extremities. Musculoskeletal and neurologic examinations were within normal limits. Funduscopic examination revealed normal eye grounds, except for some mild arteriolar narrowing. Laboratory studies revealed: fasting plasma glucose, 6.10 mmol/liter; serum cholesterol, 7.12 mmol/liter; high-density lipoprotein cholesterol, 0.70 mmol/liter; low-density lipoprotein cholesterol, 6.00 mmol/liter; and serum triglycerides, 2.10 mmol/liter. A complete blood count, as well as tests for serum...
creatinine, uric acid, and electrolytes, were normal, as was urinalysis. An electrocardiogram was normal. Ultrasound examinations of the heart and kidneys were unremarkable. Fasting plasma insulin concentration was 25 μU/ml, above the upper normal limit for normotensives in our laboratory (20 μU/ml). The patient underwent an oral glucose tolerance test after ingestion of a drink containing 40 g glucose/m² body surface. The two-hour glucose and insulin concentrations were above the upper limit of normal in controls (glucose, 7.8 mmol/liter; insulin, 50 μU/ml).

The patient began a sodium chloride- and fat-restricted diet, and lisinopril (10 mg once daily) was prescribed. Over the ensuing six months, her blood pressure was 146/95 mm Hg. At that time, laboratory examination showed: fasting plasma glucose, 5.50 mmol/liter; serum cholesterol, 6.95 mmol/liter; serum triglycerides, 1.80 mmol/liter; and fasting plasma insulin, 16 μU/ml. Pravastatin, a lipid-lowering drug, was begun, and the lisinopril dose was increased to 20 mg once daily. After one year of treatment, her blood pressure was below 140/90 mm Hg, and the blood metabolic parameters were within normal limits, that is, glucose, 5.30 mmol/liter; cholesterol, 6 mmol/liter; triglycerides, 1.50 mmol/liter; and insulin, 14 μU/ml.

**DISCUSSION**

**Dr. Javier Díez (Professor of Medicine and Director, Vascular Pathophysiology Unit, School of Medicine, University of Navarra, Pamplona, and Professor of Medicine, School of Medicine, University of Zaragoza, Zaragoza, Spain):** These two patients illustrate some of the most relevant pathophysiological features of essential hypertension. The first patient exhibited cardiac and renal damage, as evidenced by the presence of concentric left-ventricular hypertrophy (LVH) and microalbuminuria, respectively. The second patient had one of the metabolic patterns most frequently found in hypertensives: impaired glucose tolerance and hyperinsulinemia (during fasting and after a glucose challenge) associated with lipid disturbances (increased low-density lipoprotein cholesterol and triglycerides, and decreased high-density lipoprotein cholesterol). Interestingly, administration of the angiotensin-converting enzyme (ACE) inhibitor lisinopril was associated with regression of the left-ventricular mass and lessening of the microalbuminuria in the first patient and with a decrease of the plasma insulin levels in the second patient.

It is now accepted that humoral factors, that is, vasoactive substances, hormones, growth factors, and cytokines, participate directly in the development of end-organ damage and metabolic alterations that occur in hypertension. Several recent findings have underscored the potential participation of insulin-like growth factor I (IGF-I or somatomedin C) in the development of cardiac and renal damage in patients with essential hypertension. These findings include the ability of IGF-I to directly promote cardiac growth [1] and glomerular alterations [2] and its ability to regulate glucose metabolism [3].

In this Nephrology Forum, I will review the most prominent data on the biochemistry and biologic actions of IGF-I, with a special focus on the physiologic effects of the factor on the cardiovascular system. Also, I will address the evidence suggesting that alterations in the synthesis, secretion, and/or tissue bioavailability of IGF-I participate in the pathophysiology of essential hypertension. Finally, I will propose that some of the beneficial effects produced by ACE inhibitors are related to their capacity to modify the production and/or the tissue bioavailability of IGF-I in hypertensive patients.

**Biochemistry and physiology of IGF-I**

Insulin-like growth factor I belongs to a family of single-chain polypeptides (IGF-I and IGF-II) with structural homology to proinsulin [4]. Insulin-like growth factor I consists of 70 amino acid residues with a predicted molecular weight of 7649 Da; IGF-II consists of 67 amino acids and has a predicted molecular weight of 7469 Da. Comparison of the primary sequences of the IGFs allows recognition of B, C, and A domains, as in pro-insulin. In addition, the IGFs have a carboxy-terminal extension (D domain) not present in pro-insulin. Insulin-like growth factors are 70% identical to one another, and their A and B domains are 50% identical to the A and B chains of human insulin.

The human IGF-I gene has been mapped to the long arm of chromosome 12 [5]. It comprises at least five exons spread over more than 90 kbp. The gene encodes two precursor forms of IGF-I, represented by transcripts with distinct 3’ regions. The resulting precursor forms of IGF-Ia and IGF-Ib differ in the terminal portion of their carboxy-terminal peptides. Regulation of IGF-I gene expression can occur at several sites, namely, gene transcription, RNA processing and transport, and mRNA stability, as well as during post-translational events.

The circulating IGF-I is synthesized primarily by the liver under the control of growth hormone (GH). The interaction of GH with its hepatic receptor stimulates expression of the IGF-I gene and release of IGF-I peptide [6]. Serum concentrations of IGF-I usually parallel 24-hour mean serum concentrations of GH, and IGF-I inhibits the secretion of GH by the pituitary. Many other factors control blood IGF-I concentrations as well (Table 1).

Besides the liver, many other organs produce IGF-I [7]. Growth hormone, parathyroid hormone, glucocorticoids, and sex steroids regulate the local production of IGF-I. Sara and Hall have proposed that intact IGF-I, which is bound by IGF-binding proteins (IGFBPs), represents the endocrine form of IGF-I present in the circulation [8]. Truncated IGF-I, which is present in tissues and which displays weak affinity of binding to IGFBPs, represents the locally acting autocrine or paracrine form of IGF-I. According to this model, a protease that trun-
Table 1. Factors that control circulating insulin-like growth factor-I concentrations

<table>
<thead>
<tr>
<th>Factor</th>
<th>Impact on circulating IGF-I</th>
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<tr>
<td><strong>Main factors</strong></td>
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<tr>
<td>GH</td>
<td>Serum concentration of GH usually parallels 24-hour concentration of IGF-I</td>
</tr>
<tr>
<td>IGF-I</td>
<td>IGF-I suppresses GH secretion by pituitary and indirectly controls its own secretion</td>
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<td><strong>Demographic factors</strong></td>
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<tr>
<td>Age</td>
<td>Peak at adolescence</td>
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<tr>
<td>Gender</td>
<td>Females exhibit concentrations 20% more than males</td>
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<tr>
<td>Pregnancy</td>
<td>IGF-I concentrations are highest during the third trimester</td>
</tr>
<tr>
<td>Nutritional status</td>
<td>Fasting causes 70% decline in IGF-I levels in 10 days</td>
</tr>
<tr>
<td><strong>Other hormonal factors</strong></td>
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<tr>
<td>Thyroxine</td>
<td>IGF-I concentrations decrease in hypothyroidism</td>
</tr>
<tr>
<td>Prolactin</td>
<td>In the absence of GH, prolactin is a weak biologic stimulus of IGF-I</td>
</tr>
<tr>
<td>Estrogens</td>
<td>Physiologic estrogen replacement causes an increase in IGF-I concentrations</td>
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† GH, growth hormone; IGF-I, insulin-like growth factor I

Mohan et al recently proposed that IGFBPs also mediate IGF-independent biologic effects [11]. For example, IGFBP-1 stimulates vascular smooth muscle cell (SMC) migration in an IGF-independent manner involving binding to integrin receptors [12].

The IGF-I receptor (IGF-IR) is a heterotetrameric glycoprotein composed of two ligand-binding α-subunits of 706 amino acids and two transmembrane β-subunits of 627 residues [13]. The human protein is produced by mRNAs derived from a single 21-exon IGF-IR gene located on chromosome 15q25-q26. The α-subunit contains the ligand-binding region of the receptor. The IGF-IR binds IGF-I with a dissociation constant (Kd) of less than 1 nm in intact cells; IGF-II binds with several-fold lower affinity, and insulin with more than 100-fold lower affinity [14]. In general, biologic potency parallels binding affinity. The β-subunit is composed of a short extracellular domain, a membrane-spanning segment, and a large intracytoplasmic region containing a tyrosine kinase domain and sites of tyrosine and serine phosphorylation [14].

Stimulation of IGF-IR by ligand binding activates the intracellular tyrosine kinase and leads to rapid tyrosine phosphorylation of insulin receptor substrate and to intracytoplasmic assembly of a complex consisting of a variety of proteins that are responsible for stimulation of diverse downstream signal transduction pathways [14]. These events then induce several biologic actions, including stimulation of hormone-sensitive glucose transport [15] and activation of proteins involved in cell growth, differentiation, and survival [16].

**Actions of IGF-I potentially relevant to the pathophysiology of hypertension**

The GH/IGF-I axis is primarily involved in the regulation of somatic growth, but it also participates in the

![Fig. 1. Distribution of circulating insulin-like growth factor I (IGF-I) among its different binding proteins (IGFBPs) and access to its target tissues. Symbols are: (○) IGF-I; (■) IGFBP-3; (▲) ALS, (□) IGFBP-1. The interaction of IGF-I with its receptor (IGF-IR) leads to several biologic effects, including glucose uptake and cell growth, differentiation, and survival.](image-url)
Insulin-like growth factor I mRNA expression is increased in the myocardium of both pressure- [21] and volume-overloaded [22, 23] animals and rats with spontaneous hypertension (SHR) [24]. Furthermore, increased cardiac expression of IGF-I and its receptor also might be required to produce the hypertrophic response of the heart to the increased arterial load associated with systemic hypertension [25].

In addition, various observations suggest that IGF-I functions as a survival factor by preventing the programmed cell death of many cell types [16], including cardiac myocytes [26]. Insulin-like growth factor I-mediated inhibition of apoptosis is associated with increased expression of a member of the anti-apoptosis family of Bcl-2 proteins [27]. Interestingly, Bcl-2 expression is increased over normal in several cell types in the hypertrophied left ventricle of adult SHR rats [28, 29]; this model exhibits increased apoptosis of left-ventricular cardiac myocytes [30]. Thus, the possibility exists that IGF-I helps maintain myocardial cell survival in hypertensive cardiac hypertrophy via stimulation of the Bcl-2 family of proteins.

In vitro [31] and in vivo [32] data have established that IGF-I is a smooth muscle cell (SMC) mitogen. In addition, a number of findings suggest that IGF-I mediates the SMC growth response to different mechanical and humoral stimuli. Increased SMC IGF-I expression, at both the mRNA and protein levels, is associated with the development of SMC hypertrophy and hyperplasia during elevation in vascular wall stress [33, 34]. Nonhemodynamic factors that stimulate SMC growth, including growth factors such as platelet-derived growth factor [35], vasoactive substances such as angiotensin II [36], and reactive oxygen species [37], also induce IGF-I expression in these cells. Thus, IGF-I may be an important link in mediating structurally adaptive growth responses in the blood vessel wall.

In rats, administration of IGF-I decreases blood pressure, a response mediated by nitric oxide (NO) [38]. In vitro experiments have confirmed that NO is an important mediator of IGF-I–induced vascular relaxation [39]. In cultured endothelial cells, IGF-I stimulates endothelial NO synthase (eNOS)–mediated NO production [40]. In addition, Walsh and colleagues have shown that IGF-I stimulates inducible NO synthase (iNOS)–mediated NO production in cultured SMCs [41]. Therefore, IGF-I might play a role in the regulation of blood pressure and regional blood flow via NO.

Transgenic mice overexpressing GH also have elevated IGF-I levels. In these animals, glomerular enlargement and sclerosis develop as the result of increased glomerular production of extracellular matrix proteins [42, 43]. However, mice transgenic for IGF-I also have increased glomerular size but do not develop accelerated glomerular sclerosis, even though serum IGF-I levels in

<table>
<thead>
<tr>
<th>Site of action</th>
<th>Action and potential consequence</th>
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<tbody>
<tr>
<td>Heart Myocytes</td>
<td>Induction of hypertrophy and promotion of cell survival that might contribute to development of LVH.</td>
</tr>
<tr>
<td>Vasculature Endothelial cells</td>
<td>Stimulation of NO production that might participate in regulation of BP and regional blood flow.</td>
</tr>
<tr>
<td>Smooth muscle cells</td>
<td>Stimulation of NO production that might participate in regulation of BP and regional blood flow.</td>
</tr>
<tr>
<td>Kidney Vascular cells</td>
<td>Stimulation of NO production that might determine pregglomerular vasodilatation and increase of GFR.</td>
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<tr>
<td>Mesangial cells</td>
<td>Stimulation of NO production that might determine mesangial relaxation and increase of Kf.</td>
</tr>
<tr>
<td>Tubular cells</td>
<td>Stimulation of NO production that might determine mesangial relaxation and increase of Kf.</td>
</tr>
<tr>
<td>Other Skeletal muscle cells</td>
<td>Stimulation of glucose uptake via IGF-IR that leads to diminished secretion of insulin and lowers insulinemia.</td>
</tr>
<tr>
<td>Fibroblasts</td>
<td>Stimulation of NO production that might determine mesangial relaxation and increase of Kf.</td>
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</table>

4 LVH, left-ventricular hypertrophy; NO, nitric oxide; BP, blood pressure; GFR, glomerular filtration rate; Kf, ultrafiltration coefficient; IGF-IR, insulin-like growth factor I receptor.
IGF-I transgenic mice also were increased, as in GH transgenic animals [42, 43]. This discrepancy is difficult to explain because glomeruli do not express GH receptors and might not synthesize IGF-I in vivo. Thus, GH-induced effects on the glomerulus could only be explained by an indirect action by which GH increases systemic IGF-I, which then acts through glomerular IGF-IR [2]. This hypothesis is supported by the observation that IGF-I stimulates mRNA and secreted protein levels of different extracellular matrix proteins in cultured rat glomerular mesangial cells [44]. Studies performed in humans [45, 46] and animals [47, 48] have shown that exogenous and endogenous IGF-I raises renal plasma flow and glomerular filtration rate (GFR) but produces inconsistent effects on tubular sodium handling [2]. The renal hemodynamic actions of IGF-I seem to be secondary to a reduction in the renal efferent, and possibly afferent, arteriolar resistance [48] and might be mediated by local induction and release of NO [49]. In addition, IGF-I administration is accompanied by an increase in the glomerular ultrafiltration coefficient [48]. Although this effect can be due to the relaxation of the mesangium [50], the possibility also exists that IGF-I increases glomerular capillary permeability [2].

Many observations indicate that altered regulation of glomerular hemodynamics plays a critical role in the pathophysiology of hypertension [51]. Moreover, glomerulosclerosis is one of the most relevant features of clinical hypertension [52]. Thus, IGF-I emerges as a potential candidate responsible for those renal alterations in hypertension.

Several studies have demonstrated that IGF-I reduces blood glucose and serum insulin concentrations in patients with insulin resistance [see Ref. 3 for review]. How IGF-I works in patients with insulin resistance remains unclear, but the response to IGF-I in patients with mutations in the insulin-receptor gene or post-receptor defects supports the notion that IGF-I acts through mechanisms similar to, but distinct from, those of insulin itself, possibly exclusively through the IGF-IR [53, 54]. In addition, when IGF-I inhibits the secretion and lowers serum and tissue concentrations of insulin [55], peripheral tissues can upregulate their insulin receptors and become more responsive to insulin. On the other hand, IGF-I inhibits the secretion of glucagon, normally a powerful stimulus to hepatic glucose production [56].

The existence of glucose intolerance and hyperinsulinemia in almost one-half of the hypertensive population has established that resistance to insulin-stimulated glucose uptake is present in these individuals [57, 58]. Whether stimulation of glucose uptake by IGF-I compensates for the defect or defects that block the action of insulin in hypertensives without insulin resistance remains an interesting possibility.

Extracellular matrix metabolism is also affected by IGF-I. Fibroblasts are both a source of IGF-I and a target for this growth factor. Insulin-like growth factor I stimulates fibroblast proliferation and increases synthesis of fibrillar collagen types I and III [59]. Accordingly, biochemical evidence of increased synthesis of fibrillar collagen has been found in acromegalic patients with increased circulating levels of IGF-I [60]. Furthermore, synthesis of fibrillar collagen returns to normal in acromegalic patients treated with octreotide, a drug that normalizes IGF-I levels by reducing GH secretion [61].

A substantial increase in fibrillar collagen has been observed in the cardiac ventricles and the arterial wall of animals and humans with arterial hypertension [62, 63]. This fibrosis is the result of both increased collagen types I and III synthesis by fibroblasts and unchanged or decreased extracellular collagen degradation [64]. Besides hemodynamic factors, nonhemodynamic factors, that is, growth factors and vasoactive substances, can be involved in the disequilibrium between collagen synthesis and degradation that occurs in hypertension [65]. Thus, an excess of IGF-I also might promote the exaggerated synthesis of fibrillar collagen in hypertensive patients as in acromegalic patients.

### Table 3. Levels of insulin-like growth factor I (IGF-I) and growth hormone (GH) in normotensive control subjects and hypertensive patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls (N=30)</th>
<th>Hypertensives (N=47)</th>
<th>Lower limit in acromegaly</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-I (ng/ml)</td>
<td>119 (88–155)</td>
<td>192 (100–287)*</td>
<td>400</td>
</tr>
<tr>
<td>GH (μg/liter)</td>
<td>0.35 (0.22–1.05)</td>
<td>0.83 (0.56–1.49)*</td>
<td>2</td>
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\* P < 0.01, versus controls. Values are given as means and range
\* P < 0.05, versus controls

**Role of IGF-I in human hypertension**

Quantitative alterations of the GH/IGF-I/IGFBP axis. Circulating levels of IGF-I are increased in patients with essential hypertension compared with those in normotensive subjects (Table 3) [66, 67]. Although abnormally high compared to normals, the levels of IGF-I in hypertensives are well below the established lower limit in patients with active acromegaly [68].

As I said previously, the liver is the major source of circulating IGF-I, its hepatic synthesis being under the control of GH [6]. Although they were abnormally high [66], the GH levels of the hypertensive patients were well below values found under conditions of GH hypersecretion (Table 3) [69]. Several other factors also might influence circulating IGF-I levels (Table 1), namely, age, estrogen levels, and nutritional status, but no differences in these parameters were found between hypertensives with increased IGF-I and normotensives. Nevertheless, the increased secretion of GH does reflect the loss of IGF-I-mediated inhibition of feedback in hypertensives.
Table 4. Factors that regulate the production of insulin-like growth factor I binding protein 1

<table>
<thead>
<tr>
<th>Effect</th>
<th>Factor</th>
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<tbody>
<tr>
<td>Stimulation</td>
<td>Major influence</td>
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<tr>
<td></td>
<td>Glucagon</td>
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<tr>
<td></td>
<td>Cortisol</td>
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<tr>
<td></td>
<td>IGF-I</td>
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<tr>
<td>Minor influence</td>
<td>Calorie restriction</td>
</tr>
<tr>
<td></td>
<td>Hyperestrogenemia</td>
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<tr>
<td></td>
<td>Tumor necrosis factor-α</td>
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<td></td>
<td>Catecholamines</td>
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<td></td>
<td>LDL-cholesterol?</td>
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<tr>
<td>Inhibition</td>
<td>Major influence</td>
</tr>
<tr>
<td></td>
<td>Insulin</td>
</tr>
<tr>
<td></td>
<td>Growth hormone</td>
</tr>
<tr>
<td>Minor influence</td>
<td>Aging</td>
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</table>

*IGF-I, insulin-like growth factor I; LDL, low-density lipoproteins

Therefore, the regulation of the GH/IGF-I axis in patients with essential hypertension is abnormal.

We reported that the ratio of IGFBP-3 and IGFBP-1 is altered in the serum of patients with essential hypertension [70]. However, because these binding proteins were examined by Western ligand blotting, quantitative interpretation of this qualitative or, at best, semiquantitative method could not be performed. Thus, in a further study we analyzed the serum concentrations of these two IGFBPs by specific radioimmunoassay [71]. Whereas the concentration of IGFBP-3 was unchanged, the concentration of IGFBP-1 in hypertensive patients was increased compared with that in normotensive controls. An abnormally high concentration of IGFBP-1 was actually observed in 53% of hypertensives. The remaining 47% of the hypertensive patients did not exhibit this alteration in the IGFBP-1 level. We also determined an indirect index of the tissue bioavailability of circulating IGF-I by calculating in each subject the ratio IGF-I × IGFBP-1: IGFBP-3. As Figure 2 shows, this index was significantly increased in hypertensives with high IGFBP-1 as compared to normotensives and hypertensives with normal IGFBP-1. Therefore, patients with high IGFBP-1 levels were considered hypertensive with an abnormally increased access to tissues of the circulating IGF-I. Patients with normal IGFBP-1 levels were termed hypertensive with normal access to tissues of the factor.

What causes the abnormally high serum level of IGFBP-1 found in approximately one-half of patients with essential hypertension? Both IGFBP-1 mRNA and protein expression have been identified in human liver and uterine decidual [72]. Results from studies in vitro and in vivo indicate that several factors regulate IGFBP-1 production in these tissues (Table 4) [72]. The available data indicate that the observed changes in the IGFBP-1 level in hypertensive patients cannot be attributed either to an excess of cortisol, glucagon, and IGF-I or to a deficit of insulin and GH. In fact, although the levels of IGFBP-1 in serum appear to be related inversely to the prevalent insulin levels, the mean levels of insulin were normal in hypertensive patients with high IGFBP-1 levels. Similarly, glucagon and cortisol levels in these patients also were within normal limits. In addition, GH and IGF-I levels were increased similarly in members of the two subgroups of hypertensive patients, those with normal IGFBP-1 levels and those with high IGFBP-1 levels. Further studies are necessary to elucidate the role of other potential mechanisms, for example, down-regulation and inhibition of protein kinase C pathway [72], in the increase in serum levels of IGFBP-1 in the approximately one-half of patients with essential hypertension.

Pathophysiologic aspects. As I previously noted, IGF-I stimulates production of NO both by endothelial cells [40] and SMC [41]. Accordingly, IGF-I might play a role in the control of blood pressure via NO. Data suggest that the ability of IGF-I to modulate the vascular NO system is decreased in some patients with essential hypertension [73].

On the other hand, Vecchione et al recently reported that IGF-I sensitization of endothelial α1-adrenergic aortic vasorelaxation is impaired in SHR as compared to normotensive Wistar-Kyoto (WKY) rats [74]. These findings suggest that the endothelium-dependent vasorelaxant actions of IGF-I can be reduced in rats and humans with genetic hypertension. Accordingly, a diminished ability of IGF-I to reduce blood pressure in
hypertensive patients might be a factor contributing to hypertension.

High IGF-I levels are associated with LVH in patients with essential hypertension [66, 67, 75, 76]. Furthermore, compared with hypertensives with normal access to tissues of IGF-I, hypertensives with increased access to tissues of the factor exhibited an increased left-ventricular mass despite similar levels of blood pressure (Fig. 3) [71]. Therefore, cardiac hypertrophy in these patients might result in part from the increased interaction of IGF-I with its cardiac receptors. In support of this possibility is the finding that IGFBP-1 transgenic mice with abnormally high serum concentrations of the protein product had a relative gain in heart weight [77]. Andronico et al have demonstrated that circulating levels of IGF-I increase in hypertensive subjects following a standard hemodynamic load (that is, standing) proportional to the increase in pressure load, measured as cardiac rate ¥ blood pressure product [78]. Furthermore, they found a positive correlation between circulating IGF-I and the activity of Na\(^+\)/Li\(^+\) countertransport in patients with essential hypertension [67]. Interestingly, Weder and coworkers have shown that Na\(^+\)/Li\(^+\) countertransport correlates positively with pressure stress on the vascular system [79]. Therefore, one can hypothesize that hemodynamic injury of the vascular wall facilitates the release of local IGF-I into the bloodstream in hypertensive patients. If this is so, the increased circulating levels of IGF-I in hypertensives could be interpreted also as a marker of vascular hypertensive damage.

We have reported an association between increased IGF-I levels and altered renal hemodynamics and function in hypertensive patients [80, 81]. We also found that hypertensives with increased tissue access of circulating IGF-I had glomerular hyperfiltration and increased microalbuminuria as compared with hypertensives with normal tissue access of the factor (Fig. 4) [71].

As previously noted, IGF-I raises GFR in normoten-
sive animals and healthy humans [45–48]. This effect has been attributed to changes in glomerular hemodynamics mediated by NO. However, Inishi and colleagues reported recently that modulation of glomerular hemodynamics by the factor is absent in SHR [82]. This finding accords with the observation that the ability of IGF-I to stimulate vascular NO is impaired in essential hypertension [73]. Thus, it is unclear whether hyperfiltration observed in hypertensives with increased tissue access of circulating IGF-I can result from an increased interaction of the factor with its receptors located in glomerular arterioles.

Several potential mechanisms have been proposed to explain the presence of increased urinary albumin excretion in patients with essential hypertension. Increased urinary albumin excretion in hypertension likely is a consequence of increased permeability of the glomerular filter, but other factors might be involved, such as the development of glomerular sclerosis [83]. As I previously mentioned, IGF-I might enhance glomerular capillary permeability [29]. In addition, IGF-I induces higher growth response and protein synthesis in mesangial cells from SHR than in mesangial cells from WKY [84]. An altered IGF-I level can contribute to metabolic derangements in hypertensive patients. Hypertensives with high IGFBP-1 exhibit lower glucose, triglyceride, and insulin levels than do hypertensives with normal IGFBP-1 (Fig. 5) [71]. In addition, compared with hypertensives with normal IGFBP-1, patients with high IGFBP-1 showed a decreased insulin:glucose ratio and decreased glucagon levels (Fig. 5) [71]. Thus, increased access to tissues of IGF-I could improve glucose metabolism in essential hypertension, a condition linked to insulin resistance [57, 58]. Our group recently confirmed this possibility [85]. We estimated both insulin resistance and β-cell function in patients with essential hypertension using the homeostasis model assessment [86]. Whereas hypertensives with high IGFBP-1 exhibited normal values of insulin resis-

Fig. 3. Mean arterial pressure and left-ventricular mass index in hypertensive patients with normal levels of insulin-like growth factor I-binding protein I (IGFBP-1) (■) and hypertensive patients with high levels of IGFBP-1 (□). Values are expressed as mean ± SEM. (Modified from Laviades et al [71] with permission.)

Fig. 4. Clearance of creatinine and urinary excretion of albumin in hypertensive patients with normal levels of insulin-like growth factor I-binding protein I (IGFBP-1) (■) and hypertensive patients with high levels of IGFBP-1 (□). Values are expressed as mean ± SEM. (Modified from Laviades et al [71] with permission.)
tance and β-cell function, hypertensives with normal IGFBP-1 exhibited abnormally high values of both these parameters. Furthermore, we noted an inverse correlation between IGFBP-1 and insulin resistance in the whole group of hypertensives. It therefore appears that increased tissue access of IGF-I counteracts the abnormal interaction of insulin with its target tissues in essential hypertension.

We also noted an association between increased serum concentrations of IGF-I and increased serum concentrations of procollagen type-III amino-terminal peptide (PIIIP) in patients with essential hypertension [87]. Fibrillar collagen type III is synthesized as a large precursor protein, procollagen type III, which has additional protein sequences (pro-peptides) at its amino-terminal and carboxy-terminal ends. Largely cleaved from the procollagen molecules before these are assembled into fibers, PIIIP then is released into the blood. Serum concentrations of PIIIP therefore could reflect the rate of synthesis of new collagen type III [88]. We believe that the finding that serum PIIIP is increased in patients with essential hypertension indicates that fibrogenic hyperactivity is present in these patients [89]. Thus, the possibility exists that an excess of IGF-I is involved in excess organ and tissue fibrogenesis in patients with essential hypertension.

ACE inhibition and the GH/IGF-I/IGFBP axis. We previously demonstrated that the ACE inhibitor captopril, but not the β-blocker bisoprolol, decreases circulating IGF-I levels in patients with essential hypertension [75]. We later showed that different ACE inhibitors can reduce circulating IGF-I levels irrespective of their chemical structures [76]. Several observations help explain the influence of ACE inhibition on IGF-I levels. In vitro and in vivo studies suggest that angiotensin II stimulates pituitary GH release both in humans and animals [90–92]. Humans acutely treated with enalapril tend to have diminished GH responses to insulin-induced hypoglycemia [93]. Urinary levels of GH decrease significantly in diabetic patients chronically treated with captopril [94]. The likelihood that ACE inhibitors diminish circulating IGF-I by suppressing the angiotensin II-dependent stimulus for GH production has been confirmed by the finding that GH levels diminish in hypertensive patients chronically treated with ACE inhibitors [75, 76].

Another aspect of interest is that the response of LVH and extracellular matrix metabolism to ACE inhibitors is related to their ability to normalize IGF-I. In fact, LVH regressed in hypertensive patients in whom the circulating levels of IGF-I were normalized after treatment with ACE inhibitors but persisted in those in whom IGF-I levels remained abnormally high after treatment, irrespective of the impact of therapy on blood pressure [75, 76]. Similarly, serum concentrations of PIIIP became normal in hypertensive patients in whom IGF-I levels decreased to normal values after treatment with lisinopril but remained abnormally high in hypertensives exhibiting increased IGF-I levels after treatment, independently of the response of blood pressure to ACE inhibition [87]. These data support the notion that ACE inhibition affects left-ventricular mass and fibrillar collagen metabolism in hypertension through inhibition of the production of circulating IGF-I.

Finally, we recently observed that long-term administration of lisinopril increases serum levels of IGFBP-1 and normalizes glucose-related parameters in patients with essential hypertension and insulin resistance at baseline [85]. Albeit preliminary, these findings reinforce the notion that tissue access of IGF-I might be one of the important factors regulating insulin sensitivity in essential hypertension. Further studies are necessary to confirm whether the improvement of insulin sensitivity reported in hypertensive patients treated with ACE inhibitors involves changes at the GH/IGF-I/IGFBP axis level.

Conclusion

In this Nephrology Forum, I have updated recent evidence strongly suggesting that alterations in the production and distribution of circulating IGF-I play a role in some pathophysiologic features of essential hypertension (Fig. 6). The liver overproduces IGF-I and IGFBP-1 under the influence of GH and unknown factors, respectively. The hemodynamic loading imposed by hypertension on the vascular wall also might facilitate the local synthesis and secretion of IGF-I. However, the lack of response of the endothelium to IGF-I can be responsible for a lack of vasorelaxant effect of the factor. An excess of circulating IGF-I coupled with an exaggerated access to its target tissues can contribute to the development of LVH and an increase in albuminuria. On the other hand, increased tissue availability of IGF-I might stimulate glucose transport by the cells, and this in turn pre-
Fig. 6. Potential involvement of insulin-like growth factor I (IGF-I) in some pathophysiological features of essential hypertension. Increased tissue availability of circulating IGF-I might facilitate the elevation of peripheral resistance and contribute to the development of cardiac and renal damage. On the other hand, it could stimulate the peripheral metabolism of glucose.

vents pancreatic hypersecretion of insulin and the metabolic abnormalities linked to insulin resistance. In view of the complexity of the GH/IGF-I/IGFBP axis, we still need answers to many questions before we will understand the exact role of the axis in the development of the end-organ damage and the metabolic disturbances associated with hypertension. The potential impact on the GH-IGF axis of antihypertensive drugs with well-described end-organ protective and metabolically favorable actions (such as ACE inhibitors) opens an interesting new dimension in the therapy of arterial hypertension. No doubt, information on this topic will increase in the near future, and a better understanding of the precise role of IGF-I in hypertension will enhance our ability to assess and treat hypertensive patients.

QUESTIONS AND ANSWERS

Dr. Nicolaos E. Madias (Chief, Division of Nephrology, New England Medical Center, Boston, Massachusetts, USA): In addition to a subpopulation of patients with essential hypertension, do patients with secondary hypertension also exhibit elevated serum IGF-I levels? Does the level of plasma renin activity influence the level of IGF-I whether in experimental or clinical hypertension?

Dr. Diéz: Acromegalic patients with hypertension also exhibit increased serum levels of IGF-I [17]. No data are available regarding serum levels of IGF-I in patients with other forms of secondary hypertension. With respect to your second question, there are no clinical data on serum levels of IGF-I in hypertensive patients classified according to the level of plasma renin activity as it relates to the concurrent rate of urinary sodium excretion. On the other hand, an increase in both left-ventricular IGF-I mRNA and protein has been described in experimental models of high- (two-kidney, one-clip Goldblatt hypertension), moderate- (uninephrectomized SHR), and low-renin (DOCA salt rats) hypertension [21–23]. The consistency of the IGF-I findings in these three models suggests that they occur independently of the systemic renin-angiotensin endocrine system. Nonetheless, a number of in vitro findings suggest that angiotensin II interacts with IGF-I at several levels in SMCs. Exposure of SMCs to angiotensin II markedly increases IGF-I mRNA [36]. Angiotensin II stimulates IGF-IR gene transcription by a protein kinase C-independent pathway [95]. Furthermore, angiotensin II induces rapid tyrosine phosphorylation of IGF-IR substrate-1 [96]. Interestingly, the angiotensin II-induced increase in DNA synthesis is almost completely abolished when SMCs are coincubated with an anti-IGF-I antibody [36]. Angiotensin II thus stimulates transcription of the IGF-I and IGF-IR genes in SMC, and the interaction of IGF-I with its receptor is required for angiotensin II-induced DNA synthesis in these cells. This interaction might have particular relevance to our understanding of the synergistic action of angiotensin II and IGF-I for promoting SMC proliferation in vivo [97].

Dr. Madias: How strong is the evidence that the serum IGFBP-1 determines the tissue accessibility of the factor? After all, altered concentrations of the IGFBPs might not necessarily imply altered distribution of IGF-I among them. Do you have information about the saturation of these IGFBPs and their affinity for IGF-I in normotension versus hypertension?

Dr. Diéz: Several potential mechanisms for enhancing
IGF-I bioavailability in the target tissues have been proposed [98]: increase of the level of free IGF-I, increase of the ratio of IGF-I to IGFBP-3, increase of the ratio of IGFBP-1 to IGFBP-3, increase of the rate of proteolysis of IGFBP-3, decrease of the rate of proteolysis of IGFBP-1, and increase of IGF-IR abundance in the target tissues. Data presented today in hypertensive patients are in agreement with the first three possibilities. Thus, it is reasonable to hypothesize that increased serum levels of IGFBP-1 determine increased transport of circulating IGF-I to its target cells in hypertensive patients with increased serum levels of IGF-I and normal serum levels of IGFBP-3. Although we have not analyzed changes in the saturation level or in the affinity of IGFBPs for IGF-I, about 75% of IGF-I in the circulation is complexed with IGFBP-3, whereas almost all the remainder of the circulating IGF-I is bound to lower molecular-mass IGFBPs, namely IGFBP-1 [9]. On the other hand, IGFBP-3 has a higher affinity for IGF-I than does IGFBP-1 (2.1 and 6.5 nm, respectively) [99]. Thus, an excess of IGFBP-1 might not be enough to modify the distribution of bound IGF-I in such a way that changes in the tissue access of the factor result. However, findings by Hardouin et al in patients with different alterations of the GH/IGF-I axis suggest that transport of circulating IGF-I to its target tissues parallels changes in the ratio between serum IGFBP-1 and serum IGFBP-3, irrespective of changes in the saturation and affinity of these IGFBPs [100].

Dr. Jesús Egido (Associate Chief, Division of Nephrology, Fundación Jiménez Díaz, and Professor of Medicine, Autónoma University, School of Medicine, Madrid, Spain): Your data suggest that in vivo growth-promoting effects of IGF-I are influenced by the level of blood pressure. Does any experimental evidence support this possibility?

Dr. Díez: Increased sensitivity to the growth-promoting effects of specific growth factors, including IGF-I, has been shown in SMCs from hypertensive animals [101]. Upregulation of IGF-IR is accompanied by increased responsiveness of SMCs to IGF-I [102]. Interestingly, several growth factors and angiotensin II increase IGF-IR in SMCs [102]. Together, these findings suggest that hypersensitivity to IGF-I mediates SMC hypertrophic and hyperplastic responses to growth factors in arterial hypertension. On the other hand, Heidenreich et al have shown that IGF-I induces higher growth response in mesangial cells from SHR than in mesangial cells from WKY rats [84]. These authors also demonstrated that changes of cytosolic free-calcium concentration were not associated with increased responsiveness of SHR mesangial cells to IGF-I [84]. In this regard, it is possible that the tyrosine kinase activity of growth factors is crucial for mesangial cell mitogenicity rather than effects on cytoplasmic calcium [103]. Whatever the mechanism involved in the increased sensitivity of SHR mesangial cells to the growth-promoting effect of IGF-I, that same mechanism may be involved in the pathogenesis of the glomerular alterations seen in hypertension, that is, glomerulosclerosis.

Dr. Madias: Just as is the case for IGF-I, about 50% of patients with essential hypertension have an overactive Na+/H+ exchanger in their blood cells. This phenotype is associated with a number of adverse cardiorenal manifestations. What do we know about the relationship between IGF-I and the Na+/H+ exchanger? Do patients with high access to tissues of IGF-I also have an overactive Na+/H+ exchanger? Do mice transgenic for IGF-I overexpress the Na+/H+ exchanger?

Dr. Díez: Recently, Andronico et al reported a positive correlation between circulating IGF-I and the activity of erythrocyte Na+/Li+ countertransport in patients with essential hypertension [67]. Hypertensives with increased Na+/Li+ countertransport activity have a worse cardiovascular risk profile than do hypertensive patients with normal Na+/Li+ countertransport [104]. Canessa has proposed that Na+/Li+ countertransport represents a mode of functioning of the cell membrane Na+/H+ exchanger [105]. Increased Na+/Li+ countertransport therefore could reflect an overactive Na+/H+ exchanger. On the other hand, recent papers reported that IGF-I stimulates Na+/H+ exchanger activity in SMCs [106, 107]. Since IGF-IR are present in erythrocytes, it is tempting to speculate that an excess of IGF-I results in overactivity of the erythrocyte Na+/Li+ exchanger in hypertension. Nevertheless, since no data are available on the expression of the Na+/Li+ exchanger in IGF-I transgenic mice, that hypothesis remains to be tested.

Dr. José L. Rodicio (Chief, Division of Nephrology, “12 de Octubre” University Hospital, and Professor of Medicine, Complutense University, School of Medicine, Madrid): Your findings indicate that IGFBP-1 is involved in insulin resistance in patients with essential hypertension. Do data support a glucoregulatory role for this protein?

Dr. Díez: Possible evidence of the glucoregulatory role of IGFBP-1 is seen in fasting healthy subjects following a single injection of recombinant human IGF-I, which elicits a profound acute increase in serum IGFBP-1 levels, accompanied by a marked suppression of insulin levels and a 20% decline in blood glucose [108]. The peak IGFBP-1 response at six hours is strongly associated with the peak glucose response at eight hours. Thus the insulin-like activity of IGF-I, in conditions in which insulin secretion is greatly suppressed, might be closely regulated by IGFBP-1 [108].

Dr. Rodicio: You found that serum levels of IGFBP-1 are inversely related to insulin resistance in patients with essential hypertension. Do you know other clinical conditions in which a similar association has been found?
Dr. Díez: Polycystic ovary syndrome also is characterized by insulin resistance. Morris and Falcone found that serum IGFBP-1 concentrations related positively to insulin sensitivity ($r = 0.76, P < 0.003, N = 15$) in this condition [109]. Furthermore, IGFBP-1 concentration remained a significant predictor of insulin sensitivity when controlled for the body mass index in these women.

Dr. Fernando Valderrábano (Chief, Department of Nephrology, Gregorio Marañón University Hospital, and Professor of Medicine, Complutense University School of Medicine): You have proposed a role for IGF-I in insulin resistance associated with essential hypertension. Do you think this situation obtains in patients with chronic renal failure?

Dr. Díez: The IGF-I/IGFBP axis has been characterized in patients with chronic renal failure [see Ref. 2]. Most investigators found normal serum IGF-I and increased serum IGFBP-1 and -3 levels in patients with chronic renal failure. On the other hand, we have long known that patients with chronic renal failure are resistant to the effects of IGF-I on protein anabolism [110]. Studies carried out by Ding and associates strongly suggest that the IGF-I resistance in chronic renal failure is caused, at least in part, by an IGF-I post-receptor defect [111]. However, Mak recently reported that the ability of IGF-I infusion to stimulate total-body glucose uptake is maintained in rats with chronic renal failure that are insulin resistant [112]. It is therefore unclear how changes in tissue accessibility and actions of IGF-I participate in the multifactorial origin of insulin resistance in chronic renal failure.

Dr. Egido: From your findings, it appears that treatment with an ACE inhibitor increases the serum level of IGFBP-1. Do you have any information on the potential ability of angiotensin II to regulate IGFBP synthesis?

Dr. Díez: In fact, we recently observed that chronic administration of the ACE inhibitor lisinopril is associated with a significant increase in serum levels of IGFBP-1 in patients with essential hypertension [85]. This effect appears to be independent of the hemodynamic effect of the drug. Thus, the increase might be related to the ACE inhibition. Whereas angiotensin II infusion reduces serum IGFBP-3 levels and increases serum IGFBP-2 levels in rats, no changes have been observed in the serum levels of other IGFBPs, including IGFBP-1 [113]. The possibility therefore exists that changes in serum IGFBP-1 levels after lisinopril treatment are unrelated to a reduced availability of angiotensin II but relate to changes in other active fragments of angiotensin II—that is, angiotensin II (1–7), angiotensin III, angiotensin IV—or increased availability of bradykinin-related products.

Dr. Santiago Lamas (Senior Investigator, Center for Biological Research, High Council for Scientific Research, Madrid): You mentioned that IGF-I stimulates eNOS-mediated NO production by endothelial cells. Could you elaborate on the molecular mechanisms involved in such an effect? Can IGF-I also regulate the inducible form of NOS?

Dr. Díez: In fact, stimulation with IGF resulted in a rapid, dose-dependent increase in NO in cultured human umbilical vein endothelial cells and cultured immortalized rat renal interlobar artery endothelial cells [40]. The effect of IGF-I was suppressed by pretreatment with anti-IGF-I antibody, suggesting that it was specific for IGF-I. An inhibitor of NO synthesis, Nω-nitro-L-arginine methyl ester significantly blunted the responses to IGF-I, but dexamethasone preincubation did not reduce the IGF-I-induced release of NO. These results indicate that the observed IGF-I-induced release of NO is a result of activation of the constitutive, rather than the inducible, type of eNOS. Genistein, a tyrosine kinase inhibitor, profoundly suppressed the IGF-I-induced release of NO, but IGF-I did not affect the cytosolic concentration of calcium in either type of cells. Therefore, IGF-I–induced NO production by both types of endothelial cells is mediated via a tyrosine kinase–dependent mechanism. Discrepant data have been reported concerning the potential effects of IGF-I on the inducible form of NOS. Schini et al found that IGF-I inhibits cytokine-mediated induction of NOS expression and activity in SMCs [114]. In contrast, Walsh et al reported that IGF-I stimulates inducible NOS-mediated NO production in SMCs [115]. Since methods used in the two studies were different, further studies are necessary to clarify the real impact of IGF-I on inducible NOS.

Dr. Egido: A number of in vitro studies have shown that IGF-I inhibits apoptosis. Have you any information on the ability of IGF-I to block apoptosis in vivo?

Dr. Díez: Resnicoff and colleagues showed that IGF-I protects cells from apoptosis in transplanted tumors [116]. Moreover, its administration attenuates cardiomyocyte death in ischemic reperfusion injury [26]. A recent report showed that overexpression of human IGF-I in transgenic mice protects from cardiomyocyte apoptosis after infarction [117]. The mechanisms by which IGF-I prevents apoptosis are unknown, but the IGF-I/IGF-IR system mediates the formation of some molecules that inhibit apoptosis (that is, Bcl-2 oncoproteins) [27]. In addition, IGF-I blocks the activation of some members of the interleukin-converting enzyme family that act as an effector of apoptosis [118].

Dr. Rodicio: Would you comment on the effects of IGF-I on sodium homeostasis and tubular sodium handling?

Dr. Díez: Clinical studies suggest that pharmacologic administration of IGF-I causes edema that is transient in most normal subjects but which can be more severe in individuals who have greater than usual salt or fluid intake [see Ref. 2]. Experimental studies in cultured A6
cells suggest that IGF-I activates distal tubular apical Na\(^+\) channels [119]. Such activation could account for increased distal tubular sodium and fluid absorption. In our study, no differences in either net or fractional sodium excretion were observed between hypertensive patients with increased tissue access of circulating IGF-I and hypertensive patients with normal tissue access of circulating IGF-I [71]. It is important to note that all these patients were studied under conditions of low-moderate sodium intake (100–120 mmol/day).

**Dr. Pietro Zucchelli (Professor, Malpighi Department of Nephrology, Policlinico S. Orsola-Malpighi, Bologna, Italy):** Could increased delivery of circulating normal levels of the hormone, and normotensive individuals, suggest that IGF-I activates distal tubular apical proteins.

**Dr. Carlos Caramelo (Consultant Nephrologist, Department of Physiology, University of Salamanca, Salamanca, Spain):** You have shown that IGF-I infusion in humans and animals is associated with an increase in GFR. However, this parameter was only slightly increased in hypertensive patients with increased tissue access of circulating IGF-I also exhibited elevated levels of GH [71]. Certainly, we can speculate that the interaction of GH and IGF-I facilitates the development of tubulointerstitial fibrosis in these patients.

**Dr. José M. Lopez-Novoa (Professor and Chairman, Department of Physiology, University of Salamanca, School of Medicine, Salamanca, Spain):** As I said, the association of increased GH levels with exaggerated IGF-I levels in patients with essential hypertension suggests loss of the physiologic suppression of GH secretion by IGF-I [69]. Advancing age is associated with an apparent reduction in sensitivity to the GH-suppressive effects of IGF-I [122]. However, no differences in age were observed among hypertensive patients with increased levels of GH, hypertensives with normal levels of the hormone, and normotensive individuals [69]. Studies looking at the GH-suppressive effect of recombinant human IGF-I infusion could be useful to determine the sensitivity of GH secretion to IGF-I negative feedback in hypertensive patients.

**Dr. Ricardo Bosch (Professor, Department of Physiology, University of Alcalá de Henares, School of Medicine, Alcalá de Henares, Spain):** Are you aware of studies looking at the urinary excretion of IGF-I in patients with essential hypertension?

**Dr. Díez:** To my knowledge, no studies have investigated urinary levels of IGF-I in patients with essential hypertension. However, a recent report described significantly increased urinary IGF-I levels in patients with nondiabetic renal disease and chronic renal failure as compared to levels in patients with nondiabetic chronic renal disease and normal renal function and in healthy controls [123]. Urinary IGF-I did not correlate with serum IGF-I but demonstrated a significant negative correlation with the clearance of creatinine in nondiabetic patients [123]. These data in nondiabetic patients with renal disease suggest the possible participation of renal IGF-I in the progression of renal disease as a potential “toxic” protein for tubular cells.

**Dr. Madias:** Are there observations either in animals or humans on the effects of octreotide on the cardiovascular system and the kidneys?

**Dr. Díez:** Yes, increasing evidence supports a potential therapeutic role for the somatostatin analogue octreotide in several cardiovascular and renal pathologic conditions. For instance, suppression of GH production by octreotide in patients with acromegaly is associated with a significant regression of LVH and improvement of cardiac function [17]. On the other hand, octreotide infusion into either patients with essential hypertension [124] or hypertensive patients with type-II diabetes [125] is accompanied by a significant decrease in plasma insulin levels and an increased natriuretic response to a sodium load. Finally, in rats with streptozotocin-induced diabetes, octreotide can prevent the development of structural and functional renal damage [126].

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