Editorial

Cardiovascular Disease and Insulin-Like Growth Factor I

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The research field of cardiovascular disease in regard to growth hormone (GH) and its mitogenic mediator insulin-like growth factor I (IGF-I) has a long and distinguished history and is still intensively studied. Medline searches reveal that more than 1000 articles have appeared, demonstrating the importance of IGF-I in development of (and for lesions in) the vascular system. Still, mechanisms are insufficiently elucidated. This is obviously partly due to the complexity of the system with formation of IGF-I and its 6 binding proteins (IGFBPs), not only in the liver but also in almost all other organs (including smooth muscle cells), inducing autocrine/paracrine effects via the ubiquitous IGF-I receptor (including vascular endothelium). More than 80% of circulating IGF-I derives from the liver and acts as a true hormone: 99% bound to IGFBPs and 1% in free form, easily transgressing the capillaries.

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Studies in animals and cell cultures allow for examination of changes in expression of IGF-I and IGFBPs at the site of action, whereas clinical studies like that of Juul et al1 in this issue of Circulation are restricted to analyses of the blood-borne IGF-I system. The overwhelming majority of previous studies point to IGF-I being a mediator of atherosclerotic processes and diabetic vascular lesions. However, during the last 4 years studies have lent support to Juul et al’s results and processes and diabetic vascular lesions. However, during the studies point to IGF-I as a mediator of atherosclerotic vascular smooth muscle cells (VSMCs) and macrophages are involved. Foam cells, one of the hallmarks of atherosclerosis.

IGF-I and Vascular Smooth Muscle Cells

In the development of atherosclerosis, endothelium as well as vascular smooth muscle cells (VSMCs) and macrophages are involved. Foam cells, one of the hallmarks of atherosclerotic plaques, develop when monocyte-derived macrophages or VSMCs take up oxidized LDL (OxLDL).

In early atherosclerotic lesions, IGF-I and IGF-IR (receptor) expression is decreased in tunica intima but not in tunica media. The proapoptotic protein “Bax” showed colocalization of intracellular IGF-I in tunica media, which is of interest because apoptosis, as detected by TUNEL assay, does not occur in cells positive for OxLDL and Bax.4 This supports previous conclusions that apoptosis in VSMCs is regulated by specific gene products, local cytokines, and IGF-I, which acts as a survival factor.5

In advanced atherosclerotic plaques, the expression of IGF-I and IGF-IR is low or even absent in intimal regions with infiltration of macrophages as well as in those with a TUNEL-positive reaction. However, VSMCs in tunica media expressing high amounts of IGF-I and IGF-IR did not show excessive apoptosis.4

In vitro studies on rat VSMCs have shown that native LDL increases the expression of IGF-I concomitantly with DNA synthesis, but the effect can be downregulated by addition of antisera to IGF-I. The OxLDL has a reduced effect on the protein level of IGF-I as well as the manifestation of the IGF-IR. The combination of reduced IGF-I expression and low IGF-I bioavailability triggered by increasing level of IGFBP-4 may be one mechanism responsible for the OxLDL-induced cytotoxicity and apoptosis in VSMCs, which facilitate plaque instability and/or rupture.6

In atherosclerotic plaques, the inflammatory processes change the structural integrity and activate macrophages to produce proteases, growth factors, and cytokines such as TNF-α. In vitro studies on rat VSMCs have shown that TNF-α markedly suppresses IGF-I mRNA expression but upregulates IGFBP-3 synthesis. The effect on IGF-I was inhibited by actinomycin D, indicating that an intermediate signaling molecule or transacting factor may be required. IGFBP-3 seems to have an antiproliferative action on VSMCs because increased DNA synthesis occurred after addition of antisera to IGFBP-3. Consequently, it has been suggested that TNF-α reduces the level of IGF-I and upregulates IGFBP-3, which contribute to loss of VSMCs and plaque collapse.6

The effect of GH is mediated through IGF-I, but a direct impact on VSMCs has to be taken into consideration. Previous in vitro studies demonstrated that GH stimulated VSMC replication and production of basement membrane (BM) material, fibronectin, and type I collagen.7,8 It also appeared that incorporation of radiolabeled sulfate into proteoglycans was reduced and the carbohydrate constituent was altered.8 Such alterations may have significant influence on the stability of BM and on the admission of substances (like lipids) into VSMCs. These results are in agreement with biochemical and histomorphological informations acquired from arterial wall areas without atherosclerosis in patients with increased...
Glucose concentrations are maintained by infusing glucose. The gold standard technique for measuring insulin resistance is the hyperinsulinemic glucose clamp; this technique implies disposal in striated muscle and other insulin-sensitive tissues. Increased circulating GH concentrations are believed to increase local IGF-I in non-hepatic tissues (eg, vessels in the kidney and the eye). This hypothesis was supported in type 1 diabetic animals in which elevated renal IGF-I levels have been reported, despite low-circulating IGF-I levels. The expected effects of blocking local IGF-I generation and thus development of diabetic microvascular promoted development of inhibitors of the GH system. In this context, long-acting somatostatin analogues and specific GH receptor antagonists (GHRAs) have been in focus. Accordingly, administration of octreotide or GHRA in experimental diabetes has been shown to normalize intrarenal IGF-I levels and to decrease cardiovascular risk by increasing insulin sensitivity.

IGF-I and Restenosis

Restenosis, which is a frequent complication after angioplasty, is characterized by accumulation of VSMCs at the site of endothelial dilatation. There is substantial clinical and experimental evidence that IGF-I is intimately linked to the processes that result in accumulation of VSMCs. Grant and colleagues were the first to show that the concentration of IGF-I in coronary VSMCs from subjects with de novo and restenotic plaques was significantly higher than in coronary VSMCs from subjects without IHD. Furthermore, they showed that IGF-I stimulated proliferation of human coronary VSMCs in a time- and dose-dependent manner, and that the stimulatory effects of IGF-I was abolished by addition of somatostatin analogue. The pathogenic role of IGF-I has been further substantiated by experimental in vivo models showing that the VSMCs at the site of injury exhibit an increased expression of IGF-I.

To avoid restenosis and improve clinical outcome of PTCA, interest has focused on use of somatostatin analogues. This class of pharmacae suppresses IGF-I synthesis locally as well as systemically, and although this is probably an important effect when it comes to inhibiting growth of VSMCs, they also stimulate the synthesis of IGFBP-1, a potent inhibitor of IGF-I effects. In animals, systemic administration of somatostatin analogues reduced growth as well as IGF-I synthesis in VSMCs at the site of balloon injury. However, placebo-controlled trials have yielded less clear results. One study observed a reduction in angiographically documented restenosis, but failed to document an improved clinical outcome. Another study observed a significant effect of lanreotide on clinical outcome, but failed to document any effect on angiographic results. The most recent study, performed in 1997, also failed to show any beneficial effects of octreotide. The reasons for the equivocal results are not clear, but application of different doses and treatment regimes most likely explain part of the discrepancy. In our opinion, the idea of a possible beneficial effect of suppressing local IGF-I in VSMCs after angioplasty is still viable.

IGF-I and Insulin Resistance

Insulin resistance is defined as a subnormal biological response to insulin exposure and may be observed at the cellular level, in intact tissues, or at the whole body level. Most often the term insulin resistance is used to signify resistance to the actions of insulin on glucose metabolism, ie, an inadequate suppression of endogenous glucose production in liver and kidney and an inadequate stimulation of glucose disposal in striated muscle and other insulin-sensitive tissues. The gold standard technique for measuring insulin resistance is the hyperinsulinemic glucose clamp; this technique implies that a fixed dose of insulin is administered and normal glucose concentrations are maintained by infusing glucose. The glucose infusion rate (M-value) reflects insulin sensitivity and is an inverse measure of insulin resistance.

Increasing evidence has linked insulin resistance with hypertension, obesity, dyslipidemia, and cardiovascular disease. The concurrence of these abnormalities has been coined the insulin resistance syndrome or the “metabolic syndrome.”

IGF-I may interact with insulin activity in several fashions: through high-affinity binding to its own receptor or through low-affinity binding to insulin receptors. IGF-I given to human subjects increases insulin sensitivity, although unphysiologically high concentrations of free IGF-I may have prevailed. IGF-I therapy with type 1 diabetic adolescents for 24 weeks improved insulin sensitivity. Finally, hepatic IGF-I gene deletion induces insulin resistance in mice. Supporting the concept that IGF-I promotes insulin action, a recent study concluded that low concentrations of IGF-I in the circulation increased the risk for developing type 2 diabetes considerably during a 4.5-year follow-up in 615 participants.

A number of issues, however, remain uncertain. For instance, circulating IGF-I interacts with both insulin and GH secretion, and the role of free versus bound IGF-I needs clarification.

It is still a distinct possibility that one mechanism whereby IGF-I may decrease cardiovascular risk is by increasing insulin sensitivity. In addition, recent evidence indicates that the effects of GH (and thereby of IGF-I) may be U-shaped, as for instance, indicated by the fact that low levels induce insulin resistance and cardiovascular disease as seen in GH deficiency and obesity, but also high levels as seen in acromegaly.

GH/IGF and Microangiopathy

Data on the vascular effects of GH/IGF-I in vivo have been attained in animal models as well as in humans. These studies focused mainly on the potential role of GH/IGF-I in microvascular (ie, kidney and eye) diabetic complications and nondiabetic retinopathy.

It was demonstrated in 1970 that diabetic patients hypersecrete GH. At the same time the “GH-hypothesis” was launched, suggesting that GH plays an important role in the development of diabetic microangiopathy. The history of IGFs and diabetes appears to be much shorter, but more than 3 decades ago low levels of sulfation factor or nonsuppressible insulin-like activity were reported in diabetic patients without awareness of their partial identity with IGFs. It is generally believed that the pattern of GH hypersecretion and low circulating IGF-I in diabetes is caused by a decrease in hepatic IGF-I formation and serum IGF-I levels, which then secondarily induce GH hypersecretion through feedback. Increased circulating GH concentrations are believed to increase local IGF-I in non-hepatic tissues (eg, vessels in the kidney and the eye). This hypothesis was supported in type 1 diabetic animals in which elevated renal IGF-I levels have been reported, despite low-circulating IGF-I levels. The expected effects of blocking local IGF-I generation and thus development of diabetic microvascular promoted development of inhibitors of the GH system. In this context, long-acting somatostatin analogues and specific GH receptor antagonists (GHRAs) have been in focus. Accordingly, administration of octreotide or GHRA in experimental diabetes has been shown to normalize intrarenal IGF-I levels and to...
ameliorate early renal/glomerular enlargement and urinary albumin excretion (UAE).\textsuperscript{21,22} Six months of octreotide treatment in type 1 diabetic subjects has been shown to reduce UAE,\textsuperscript{23} although no clinical trials have appeared on the effects of GHRAs on diabetic nephropathy.

The role of GH and IGF-I in diabetic retinopathy is controversial, although discussed intensively for decades. Several descriptive studies have suggested a pathogenic role of the GH/IGF-axis; however, most (small) clinical trials in which diabetic subjects were treated with either octreotide or GHRA have been disappointing with no amelioration of progressive diabetic retinopathy.\textsuperscript{24} Other studies have examined the role of GH and IGF-I in nondiabetic, ischemia-induced retinal vascularization and retinopathy of prematurity (ROP). In transgenic mice expressing a GHRA gene, retinal neovascularization was inhibited, despite an elevation of vascular endothelial growth factor receptor expression, indicative of an important pathogenic role of GH (and local IGF-I).\textsuperscript{25} However, octreotide administration in rats developing ischemia-induced neovascularization has no impact on the severity of retinal changes.\textsuperscript{26} In a recent study, infants with ROP showed a prolonged period of low serum IGF-I levels, suggesting that sustained low circulating IGF-I is a significant risk factor for development of ROP.\textsuperscript{27} In the same study, the role of IGF-I in normal retinal development was studied in IGF-I knockout mice, in which the lack of IGF-I was associated with impaired retinal endothelial cell development and survival.\textsuperscript{28}

Finally, Dunger’s group\textsuperscript{28} presented very recently prospective data in type 1 diabetic children followed with annual blood sampling during 10 years demonstrating that those with low free IGF-I had significantly higher risk of developing microalbuminuria.

The article by Juul and associates\textsuperscript{1} is the first prospective study to describe an association between circulating IGF-I/IGFBP-3 and the later occurrence of ischemic heart disease. No doubt it will be found provocative and contrary to previous beliefs of many. We have attempted to review the evidence in various vascular lesions and found recent good support for the authors’ interpretations. We expect that they will raise heated and interesting discussion.

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