The Role of Growth Hormone, Insulin-Like Growth Factors (IGFs), and IGF-Binding Proteins in Experimental Diabetic Kidney Disease

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Early renal changes in type I diabetes are characterized by an increase in renal size, glomerular volume, and kidney function, and later by development of mesangial proliferation, accumulation of glomerular extracellular matrix, and increased urinary albumin excretion (UAE). Growth hormone (GH) and insulin-like growth factors (IGFs) have a long and distinguished history in diabetes mellitus, with possible participation in the development of long-term complications. In experimental diabetes in dwarf rats with isolated GH and IGF-I deficiency, a slower and lesser renal and glomerular hypertrophy is observed as compared with diabetic control animals with intact pituitary. Furthermore, diabetic dwarf rats with a diabetes duration of 6 months display a smaller increase in UAE, indicating that GH and IGF-I may be involved in the development of diabetic kidney changes. In line with this, administration of octreotide to streptozotocin (STZ)-diabetic animals with normal pituitary inhibits initial renal growth without affecting blood glucose levels, and 6 months' administration of octreotide to diabetic rats reduces long-term renal/glomerular hypertrophy and UAE. In addition, the initial increase in renal size and function in experimental diabetes is preceded by an increase in renal IGF-I, IGF-binding proteins (IGFBPs), and IGF-II/mannose-6-phosphate receptor (IGF-II/Man-6-P receptor) concentration. Finally, specific changes occur in renal GH-binding protein (GHBP) mRNA, IGF-I receptor mRNA, and IGFBP mRNA expression in long-term diabetes. In conclusion, the knowledge we have today indicates that GH and IGFs, through a complex system consisting of GHBP, IGFs, IGF receptors, and IGFBPs, may be responsible for both early and late renal changes in experimental diabetes.

OVERT DIABETIC NEPHROPATHY is clinically characterized by proteinuria, hypertension, and progressive renal insufficiency. The magnitude of this problem can be gauged by the fact that approximately 30% of all new cases of end-stage renal failure in the Western world until today have been attributable to diabetic nephropathy, making it one of the most common causes of end-stage renal failure. Diabetic kidney disease is characterized by an early increase in kidney size, glomerular volume, and kidney function, and later by the development of mesangial proliferation, accumulation of glomerular extracellular matrix, increased urinary albumin excretion (UAE), and glomerular sclerosis. The search for significant pathogenic mechanisms in diabetic kidney disease has focused on the early events, at the point in time when the above-mentioned pathophysiological changes take place. Several metabolic, functional, and structural renal changes in streptozotocin (STZ)-diabetic rats have fundamental similarities to those occurring in diabetic patients, and this model has accordingly been used extensively in diabetes research aiming to elucidate the pathogenesis of diabetic kidney disease.[1-16]

The term growth factor is used as a generic designation for any substance capable of inducing cellular differentiation and/or proliferation, and it embraces an ever increasing number of peptides found in the circulation and in different tissues. Growth factors have therefore attracted attention in several areas of diabetes research, including conceivable effects on the renal changes seen in experimental and human diabetes. The present review will describe the most recent evidence for a causal role of the growth hormone (GH)/insulin-like growth factor (IGF) axis in diabetic kidney disease, with emphasis on experimental diabetes, since few clinical studies have been published on this topic.

THE GH/IGF AXIS IN NORMAL KIDNEY

Members from both the GH and IGF systems are present in the kidney, ranging from mRNA expression for the GH receptor (GHR), GH-binding protein (GHBP),[17-19] IGF-I and IGF-II,[20-25] and their respective receptors, the IGF-I receptor and the IGF-II/mannose-6-phosphate receptor (IGF-II/Man-6-P receptor),[26-31] to the presence of six different classes of specific binding proteins (IGFBPs) for IGF-I and -II.[32-34] As will be described later, each member of the GH/IGF system has its specific localization in the nephron and thereby constitutes a unique system in which IGFs in the circulation and in the kidney may affect the nephron in both an endocrine and autocrine/paracrine fashion.

GHR and GHBP

In the rat, specific mRNA transcripts coding for the GHR (4.5 kilobase [kb]) and the GHBP (1.2 kb) have been demonstrated.[17-19] GHR and GHBP mRNAs have been detected in both hepatic and nonhepatic tissues, including the kidney.[17-19] By in situ hybridization, the GHR has been localized to the proximal straight tubule and the medullary thick ascending limb of Henle's loop.[35] Although originating from the same gene, GHR and GHBP transcripts are not coordinately expressed in different tissues, and the two mRNAs can be differentially regulated, implying that the GHBP per se may have a possible biological functional action at a cellular level, including both stimulatory[36] and inhibitory[19] actions.

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IGF-I and IGF-II

IGF-I and IGF-II mRNAs have been detected in rat and human kidney,[20-24] indicating the capacity in kidneys to synthesize IGF-I and IGF-II. Furthermore, IGF-I is found in high concentrations when extracted from the kidney.[21,24,25] By immunohistochemistry, IGF-I has been localized to the thin limb of Henle's loop, the distal convoluted tubule, and cortical and medullary collecting ducts,[20,24] thereby corresponding to the distribution of IGF-I mRNA by in situ hybridization.[20]

IGF-I and IGF-II/Man-6-P Receptors

Some of the biological actions of IGFs are thought to be mediated via two classes of specific cell surface receptors. The IGF-I receptor is a heterotetrameric glycoprotein with a primary structure that is highly homologous to the insulin receptor, consisting of two α- and two β-subunits linked by disulfide bridges. IGF-I and insulin receptors belong to a family of tyrosine kinases. The IGF-I receptor has been identified in the kidney on the basis of competitive binding experiments, Northern blotting, and in situ hybridization.[26-28] IGF-I receptor mRNA in rat and human kidney has been localized in glomeruli and in the tubular epithelium of the medulla, and is barely detectable in the proximal tubules.[31] However, it is evident from various studies that IGF-I receptors are widely distributed in the proximal tubules, present at both the luminal and basolateral portions of the tubular cell.[26-28] The IGF-II/Man-6-P receptor is structurally unrelated to IGF-I and insulin receptors, consisting of a single-chain transmembrane glycoprotein lacking tyrosine kinase activity.[30] In rat and human kidney, IGF-II/Man-6-P receptor mRNA has a localization similar to that of the IGF-I receptor, although it is not found in the glomeruli.[31] The IGF-II/Man-6-P receptor, in competitive binding experiments, has been found to be abundant in both glomeruli and the proximal tubule.[29,30] In a recent immunohistochemical study, the IGF-II/Man-6-P receptor has been found to be localized solely to the proximal tubule.[29]

IGFBPs

IGF-I and IGF-II are bound to specific IGFBPs in the circulation and in the extracellular space. To date, six different IGFBPs have been cloned and are designated IGFBP-1 to -6.[32,33] Under normal circumstances, IGFBP-3 is the predominant carrier of IGFs in the circulation, and one of its roles is to function as a carrier protein for IGFs, thereby protecting IGFs from degradation and sequestration and ensuring a sufficient supply to target tissues. However, it seems evident today that IGFBPs may also act as modulators of IGF actions at a cellular level, by both enhancing and inhibiting the biological actions of IGFs. All six IGFBPs are expressed in the kidney tissue.[31-34] IGFBP-1 and its mRNA have been localized to the medullary thick ascending limbs of Henle's loop and to the collecting ducts.[31,34] IGFBP-2 mRNA in both rat and human kidney has been demonstrated in glomeruli, the medullary interstitium, and collecting ducts.[31,34] IGFBP-3 mRNA is primarily localized to the cortical interstitial cells and to a lesser extent to the medullary interstitial cells.[34] IGFBP-4 mRNA is localized to the distal tubules in the cortex and to the vasculature throughout the kidney, including the vasa recta.[34] IGFBP-5 mRNA is most abundant in the medulla localized to the interstitial cells, whereas IGFBP-5 mRNA in the cortex is found in epithelial cells of both the glomeruli and distal tubules.[32,34]

THE GH/IGF AXIS IN EXPERIMENTAL DIABETIC KIDNEY DISEASE

Experimental diabetes in rats is characterized by suppressed serum levels of GH,[37,38] whereas poorly controlled diabetes in man is characterized by GH hypersecretion.[39-41] There is, on the other hand, support for the contention that the difference between experimental diabetes and human diabetes with respect to the GH/IGF axis is restricted to GH. Identical changes have been reported for other elements in the GH/IGF axis in poorly controlled diabetic rats and man, including changes in circulating levels of GHBP, IGF-I, and IGFBPs.[36,42] In addition, specific changes occur locally in the diabetic kidney, involving a number of complex cellular mechanisms with changes in renal GHBP, IGF receptors, and IGFBPs.

GHR and GHBP

Few data have been published on the renal expression of GHR and GHBP in experimental diabetes. In one study, GHR mRNA expression was measured 4 days after induction of STZ-diabetes, and unchanged levels were reported despite decreasing levels of hepatic GHR mRNA.[43] In a recent study including both short- and long-term diabetic animals, differential changes in kidney GHR and GHBP mRNA were observed.[44] In the cortex, no change was seen in GHR mRNA throughout the observation period of 6 months, whereas a significant increase in GHBP mRNA was observed after 1 month of diabetes and was sustained for the rest of the study period.[44] No changes were seen in GHR or GHBP mRNA in the medullary regions.[44] These data indicate that although GHR and GHBP mRNAs originate from the same gene, they are differentially regulated during the development of experimental diabetic kidney disease, and further imply a specific functional role for GHBP. However, whether the increase in renal GHBP mRNA actually enhances renal GH availability to the GHR and thereby enhances a pathophysiological role of GH is still unknown.

IGF-I

It is evident today that the rapid increase in renal growth and function seen in STZ-diabetes is preceded by an increase in renal tissue concentration of IGF-I, reaching a maximum at 1 to 2 days after induction of diabetes and returning to basal levels after about 4 days.[21,42,45-49] The degree of kidney IGF-I accumulation 48 hours after injection of STZ is directly proportional to the prevailing blood glucose in animals with varying degrees of metabolic control,[50] and strict insulin treatment abolishes both the increase in kidney IGF-I and the renal hypertrophy.[42,45,46] Finally, IGF-I infusion in diabetic rats commencing after the initial rapid growth rate has abated, with restoration of

the initial high kidney IGF-I levels, reaccelerates diabetic renal hypertrophy,[51] adding weight to the hypothesis that IGF-I acts as a renotropic growth factor in early experimental diabetes.

Further evidence that IGF-I, with the modulating effect of GH, may be involved in both short- and long-term renal changes is given in a series of experiments in diabetic dwarf rats and in diabetic rats treated with a long-acting somatostatin analog (octreotide). The dwarf rat strain used in these experiments is characterized by an inherited autosomally recessive gene. Homozygous dwarf rats present with an isolated GH deficiency, with approximately 5% to 10% of normal pituitary GH content, low circulating GH levels, and reduced circulating and tissue concentrations of IGF-I, but otherwise normal pituitary function.[52,53] In short-term experiments, STZ-diabetic dwarf rats exhibit slower and lesser initial renal and glomerular hypertrophy, as well as a smaller increase in kidney IGF-I, than diabetic controls with intact pituitary, indicating that GH per se may be involved in the modulation of renal enlargement.[45] Furthermore, long-term diabetic dwarf rats with a diabetes duration of 6 months display a lesser degree of renal and glomerular hypertrophy and a smaller increase in UAE as compared with pituitary-intact diabetic rats.[54] Finally, administration of octreotide to STZ-diabetic animals inhibits initial kidney IGF-I accumulation and growth without affecting blood glucose levels,[47] and, intriguingly, 6 months' administration of octreotide to diabetic rats reduces the elevated UAE, renal/glomerular hypertrophy, and serum and kidney IGF-I without affecting metabolic control.[55]

One possible explanation for the above-mentioned early renal IGF-I accumulation in STZ-diabetes may be increased local kidney IGF-I production. In support of this theory, a single report in short-term experimental diabetes has demonstrated a short-lived increase in IGF-I mRNA.[56] However, this has not been a consistent finding,[21] and in a recent long-term study (6 months) in STZ-diabetic rats, decreased renal IGF-I mRNA expression, measured by in situ hybridization, was seen from the time of diabetes induction and sustained for the whole study period.[34] These findings indicate that the increase in renal IGF-I protein is probably not due to local IGF-I production, and that renal IGF sequestration more likely may be caused by changes in renal IGF-I and IGF-II/Man-6-P receptors and IGFBPs (see below).

IGF-I and IGF-II/Man-6-P Receptors

As stated earlier, some of the biological actions of IGFs are thought to be mediated via the IGF-I and IGF-II/Man-6-P receptors. In experimental diabetes, no changes are seen in renal IGF-I receptor mRNA (Hernandez, Grønbæk, LeRoith, and Flyvbjerg, unpublished results, November 1994) or receptor binding[57] within the first days after induction of diabetes. However, it is interesting that when focusing on the later phases of diabetic glomerulopathy taking place in the months after induction of experimental diabetes, a sustained increase in kidney IGF-I receptor mRNA is seen for up to 3 months (Hernandez, Grønbæk, LeRoith, and Flyvbjerg, unpublished results, November 1994). In contrast to these results, early increased levels of both IGF-II/Man-6-P receptor protein[58] and mRNA[59] have been demonstrated within the first days after induction of diabetes. However, in long-term diabetes for up to 6 months, no changes in IGF-II/Man-6-P receptor mRNA are seen (Hernandez, Grønbæk, LeRoith, and Flyvbjerg, unpublished results, November 1994). These results therefore seem to suggest that the two structurally and functionally unrelated IGF receptors may play different roles at different time points in the development of diabetic kidney disease.

IGFBPs

Concomitantly with the increase in endogenous kidney IGF-I in early STZ-diabetes, an increase in kidney IGFBP species is seen.[60] This finding is corroborated by the finding of IGF-I binding in the diabetic kidney to low–molecular-weight material that may represent IGFBPs.[27] In a recent study describing renal IGFBP mRNA expression in both short- and long-term diabetes, prominent and complex alterations in renal IGFBP mRNA levels and distribution were seen.[34] These changes included a robust shift in the distribution of IGFBP-1 expression.[34] Immediately after induction of diabetes, medullary IGFBP-1 mRNA was drastically reduced, while cortical IGFBP-1 mRNA expression showed a pronounced increase persisting for up to 6 months.[34] In addition, a sustained increase in medullary IGFBP-5 mRNA level was seen, while cortical IGFBP-5 expression was decreased.[34] No dramatic changes were seen in IGFBP-2, -3, or -4 mRNA over the 6 months studied.[34]

The pathophysiological effects of these changes in renal IGFBP expression in diabetes are unknown. However, the striking and sustained redistribution of renal IGFBP-1 mRNA from medulla to cortex is of interest, since recent studies have suggested that some IGFBPs, in addition to acting as carriers for IGFs, also may operate as local modulators of IGF action. In particular, such mechanisms may be operative for IGFBP-1, since it contains an Arg-Gly-Asp motif near the C-terminal, which could enable it to interact with cell surfaces and deliver IGF to adjacent IGF receptors, enhancing the subsequent binding and action of IGFs on the cell.[61] However, in other studies, IGFBP-1 has been found to inhibit cellular IGF-I binding and action.[62]

The changes in IGFBP mRNA described earlier[27,34,60] occurred in the early stages of the diabetes-associated renal changes, thereby preceding the early renal and glomerular hypertrophy. Furthermore, the changes were sustained for up to 6 months after induction of diabetes, during the period when development of diabetic glomerulopathy takes place. The IGFBP mRNA changes support the notion, with respect to both duration and localization, that some IGFBPs may be involved in the development of renal changes in experimental diabetes.

SUMMARY AND CONCLUSIONS

Although it is only a little more than two decades since the characterization of GH and IGFs began in earnest, knowledge of this group of growth factors in relation to diabetic renal disease is expanding rapidly. This is mainly due to an extensive worldwide interest in the GH/IGF

Table 1. Schematic Depiction of Short- and Long-Term Changes in the Renal GH/IGF Axis in Experimental Diabetes

Renal Expression	Short-Term Diabetes	References	Long-Term Diabetes	References
GHR mRNA	Unchanged	43, 44	Unchanged	44
GHBP mRNA	Unchanged	44	Increased	44
IGF-I mRNA	Unchanged or decreased	21, 34	Decreased	34
IGF-I	Increased	21, 42, 45-49	Unchanged	55
IGF-I receptor	Unchanged	57	?	
IGF-I receptor mRNA	Unchanged	Unpublished	Increased	Unpublished
IGF-II/Man-6-P receptor	Increased	58	?	
IGF-II/Man-6-P receptor mRNA	Increased	59	Unchanged	Unpublished
IGFBP-1 mRNA	Increased	34	Increased	34
IGFBP-2 mRNA	Unchanged	34	Unchanged	34
IGFBP-3 mRNA	Unchanged	34	Unchanged	34
IGFBP-4 mRNA	Decreased	34	Decreased	34
IGFBP-5 mRNA	Increased	34	Increased	34

system in relation to the kidney, and the availability of modern molecular/cellular techniques and biosynthetically produced peptides. The knowledge we have today indicates that GH and IGFs, through a complex system of GHR, GHBP, IGFs, IGF receptors, and IGFBPs, may be responsible for both early and late renal changes in experimental diabetes (Table 1). In view of the complexity of the GH/IGF system, it will be a tremendous challenge in the coming years to fully characterize the role of the renal effects of GH/IGFs in diabetic kidney disease. However, there is no doubt that information on this topic will surface with an increasing pace in the near future, and that an understanding of the above-mentioned mechanisms will allow design of specific antagonists that may prove useful for therapeutic manipulation in the treatment of diabetic nephropathy.

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