

ACTIONS OF GROWTH FACTORS IN ACUTE RENAL FAILURE

Actions	IGF-I	EGF	↓↓
Protein	↓/↑	↑/↓	
mRNA	↓/↑	↓	
Receptors	↑	↑	
Vascular	↑	↓	
Anabolic	↑	↔	
Mitogenic	↑	↑↑↑	
Apoptosis	↓		

FIGURE 17-14

Selected actions of growth factors in the setting of acute renal failure (ARF). After an acute renal injury, a spectrum of molecular responses occur involving the local expression of growth factors and their receptors. In addition, there is considerable variation in the mechanisms by which the growth factors are beneficial for ARF. After an

acute renal insult there is an initial decrease in both insulin-like growth factor (IGF-I) peptide and mRNA, which recovers over several days but only after the regenerative process is under way. The pattern with epidermal growth factor (EGF) is different in that a transient increase in available mature peptide from cleavage of preformed EGF is followed by a pronounced and prolonged decrease in both peptide and message. Both peptide and message for hepatocyte growth factor (HGF) are transiently increased in kidney after a toxic or an ischemic insult. The receptors for all three growth factors are increased after injury, which may be crucial to the response to exogenous administration.

The mechanism by which the different growth factors act in the setting of acute renal injury is quite variable. IGF-I is known to increase renal blood flow and glomerular filtration rate in both normal animals and those with acute renal injury. To the other extreme, EGF is a vasoconstrictor and HGF is vasonutral. IGF-I has an additional advantage in that it has anabolic properties, and ARF is an extremely catabolic state. Neither EGF nor HGF seems to affect nutritional parameters. Finally, both EGF and HGF are potent mitogens for renal proximal tubule cells, the nephron segment is most often damaged by ischemic acute renal injury, whereas IGF-I is only a modest mitogen. Likewise, both EGF and HGF appear to be more effective than IGF-I at inhibiting apoptosis in the setting of acute renal injury, but it is not clear whether this is an advantage or a disadvantage.

Clinical Use of Growth Factors in Acute Renal Failure

HGF

- ↑
- ↑
- ↑
- ↔
- ↔
- ↑↑↑

FIGURE 17-15

Rationale for the use of insulin-like growth factor IGF-I in the setting of acute renal failure (ARF). Of the growth factors that have been demonstrated to improve outcomes after acute renal injury, the most progress has been made with IGF-I. From this table, it is evident that IGF-I has a broad spectrum of activities, which makes it a logical choice for treatment of ARF. An agent that increased renal plasma flow and glomerular filtration rate and was mitogenic for proximal tubule cells and anabolic would address several features of ARF.

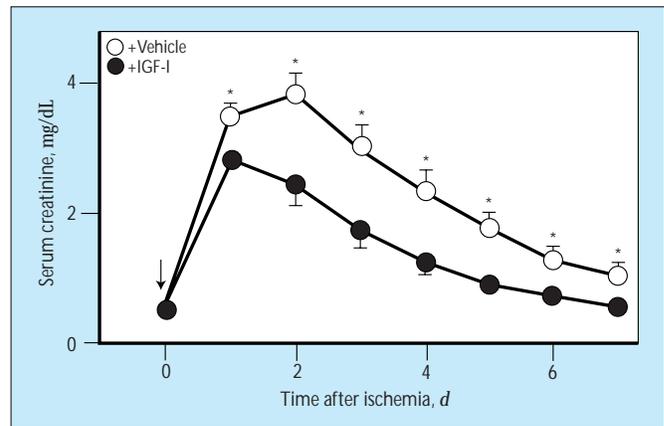
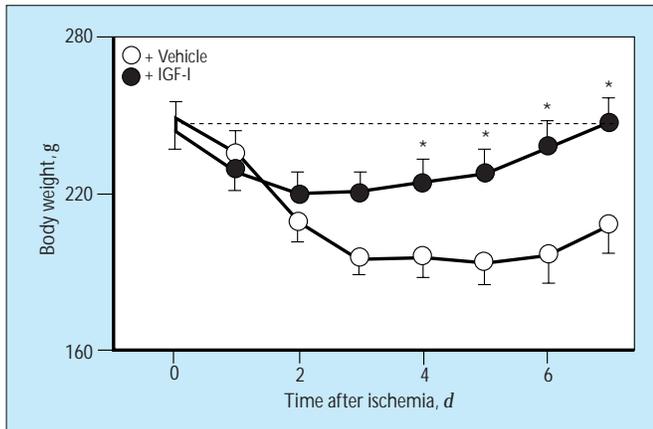


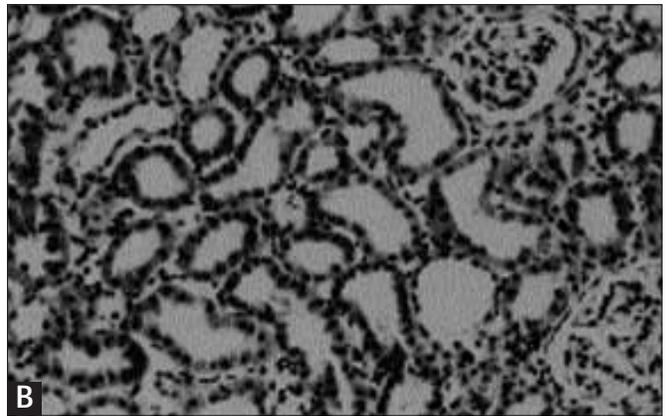
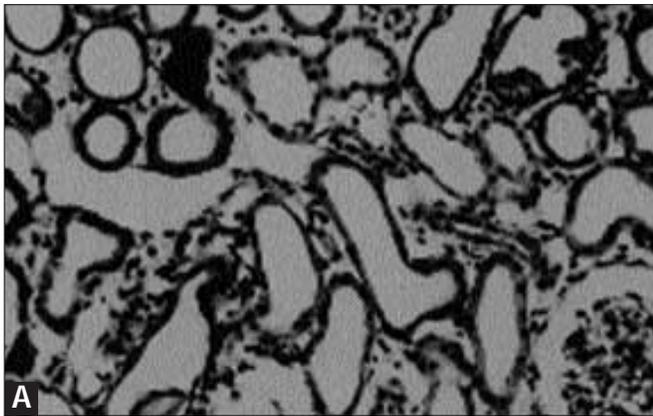
FIGURE 17-16

Serial serum creatinine values in rats with ischemic acute renal failure (ARF) treated with insulin-like growth factor (IGF-I) or vehicle. This is the original animal experiment that demonstrated a benefit from IGF-I in the setting of ARF. In this study, IGF-I was administered beginning 30 minutes after the ischemic insult (arrow). Data are expressed as mean ± standard error. Significant differences between groups are indicated by asterisks.

This experiment has been reproduced, with variations, by several groups, with similar findings. IGF-I has now been demonstrated to be beneficial when administered prophylactically before an ischemic injury and when started as late as 24 hours after reperfusion when injury is established. It has also been reported to improve outcomes for a variety of toxic injuries and is beneficial in a model of renal transplantation with delayed graft function and in cyclosporine-induced acute renal insufficiency. (From Miller *et al.* [2]; with permission.)

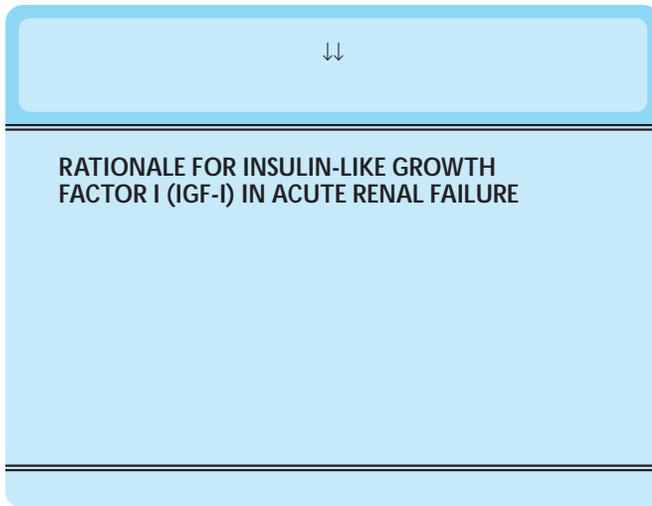
**FIGURE 17-17**

Body weights of rats with ischemic acute renal failure (ARF) treated with insulin-like growth factor (IGF-I) or vehicle. Unlike epidermal growth factor or hepatocyte growth factor (HGF), IGF-I is anabolic even in the setting of acute renal injury. These data are from the experiment described in Figure 17-16. As the data in this figure demonstrate, ARF is a highly catabolic state: vehicle-treated animals experience 15% weight reduction. Animals that received IGF-I experienced only a 5% reduction in body weight and were back to baseline by 7 days. Data are expressed as mean \pm standard error. Significant differences between groups are indicated by asterisks. (From Miller *et al.* [2]; with permission.)

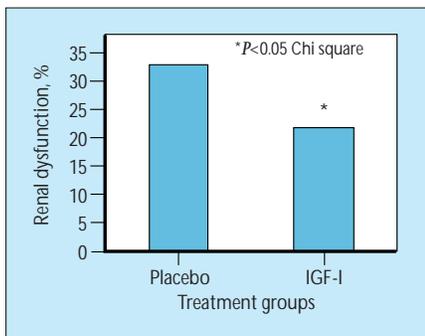
**FIGURE 17-18**

Photomicrograph of kidneys from rats with acute renal failure (ARF) treated with insulin-like growth factor (IGF-I) or vehicle. These photomicrographs are of histologic sections stained with hematoxylin and eosin originating from kidneys of rats that received vehicle or IGF 1 after ischemic renal injury. Kidneys were obtained 7 days after the insult. There is evidence of considerable residual injury in the kidney from the vehicle-treated rat (A): dilation and simplification of tubules, interstitial calcifi-

cations, and papillary proliferations the tubule lumen of proximal tubules. The kidney obtained from the IGF-I-treated rat (B) appears almost normal, showing evidence of regeneration and restoration of normal renal architecture. In this experiment the histologic appearance of kidneys from the IGF-I-treated animals was statistically better than that of the vehicle-treated controls, as determined by a pathologist blinded to therapy. (From Miller *et al.* [2]; with permission.)

**FIGURE 17-19**

Reported therapeutic trials of insulin-like growth factor (IGF-I) in humans. Based on the compelling animal data and the fact that there are clearly identified disease states involving both

**FIGURE 17-20**

Incidence of postoperative renal dysfunction treated with insulin (IGF-I) or placebo. IGF-I significantly reduced the incidence of postoperative renal dysfunction in these high-risk patients. Renal dysfunction occurred in 33% of those who received placebo but in only 22% of patients treated with IGF-I. The groups were well-matched with respect to age, sex, type of operation, ischemia time, and baseline renal function as defined by serum creatinine or glomerular filtration rate. The IGF-I was tolerated well: no side effects were attributed to the drug. Secondary end-points such as discharge, serum creatinine, length of hospitalization, length of stay in the intensive care unit, or duration of intubation were not significantly different between the two groups. (*Adapted from Franklin, et al.* [3]; with permission.)

over- and underexpression of IGF-I, this is the first growth factor that has been used in clinical trials for kidney disease. Listed above are a variety of studies of the effects of IGF-I in humans. This peptide has now been examined in several published studies of both acute and chronic renal failure. Additional studies are currently in progress.

In the area of acute renal failure there are now two reported trials of IGF-I. In the initial study IGF-I or placebo was administered to patients undergoing surgery involving the suprarenal aorta or the renal arteries. This group was selected as it best simulated the work that had been reported in animal trials of ischemic acute renal injury. Fifty-four patients were randomized in a double-blind, placebo-controlled trial of IGF-I to prevent the acute decline in renal function frequently associated with this type of surgery. The primary end-point in this study was the incidence of renal dysfunction, defined as a reduction of the glomerular filtration rate as compared with a preoperative baseline, at each of three measurements obtained during the 3 postoperative days. Modern surgical techniques have decreased the incidence of acute renal failure to such a low level, even in this high-risk group, so as to make it impractical to perform a single center trial with enough power to obtain differences in clinically important end-points. Thus, this trial was intended only to offer "proof of concept" that IGF-I is useful for patients with acute renal injuries.

Receptors are present on proximal tubules
Regulates proximal tubule metabolism and transport

Increases renal plasma flow and glomerular filtration rates
Mitogenic for proximal tubule cells
Enhanced expression after acute renal injury
Anabolic

THERAPEUTIC TRIALS OF INSULIN-LIKE GROWTH FACTOR I IN HUMANS

FIGURE 17-21

Summary of an abstract describing the trial of insulin-like growth factor (IGF-I) in the treatment of patients with established acute renal failure (ARF). Based on the accumulated animal and human data, a multicenter, double-blind, randomized, placebo-controlled trial was performed to examine the effects of IGF-I in patients with established ARF. Enrolled patients had ARF of a wide variety of causes, including surgery, trauma, hypertension, sepsis, and nephrotoxic injury. Approximately 75 patients were enrolled, treatment being initiated within 6 days of the renal insult. Renal function was evaluated by iodothalimide clearance. Unfortunately, at an interim analysis (the study was originally designed to enroll 150 patients) there was no difference in renal function or survival between the groups. The investigators recognized several potential problems with the trial, including the severity of many patients' illnesses, the variety of causes of the renal injury, and delay in initiating therapy [4].