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Uninary Plasminogen Activator Activity in Progressive Renal Failure

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The purpose of this study was to discover how functional nephrons produce the plasminogen activator as renal function progresses to renal failure. Urine Plasminogen activator (U-PA) activity was measured by the fibrin plate method in 73 patients with various degrees of renal function deterioration from various underlying diseases and in one healthy individual in order to evaluate the plasminogen activator activity of remanant nephrons. The plasminogen activator activity of the 12 consecutive urine samples from the healthy individual showed that is varied according to the time of day, but there was no circadian rhythm. The urine plasminogen activator activity correlated with the osmolality ($r=0.51$, $P<0.001$) and creatinine ($r=0.56$, $P<0.001$) of the urine, suggesting that it is concentrated at distal nephrons. The fractional sodium excretion rate (FeNa) increased abruptly when GFR decreased below 25 L/day. This pattern was very similar with the relation between total U-PA activity/GFR and GFR. The correlation between total U-PA activity and FeNa was not significant, but there was a significant direct correlation between total U-PA activity/GFR and FeNa ($r=0.775$, $P<0.0001$). There was no relationship between the 24-hour urine protein and total U-PA activity or total U-PA activity/GFR. The total urine plaminogen acvivator activity correlated with the 24-hour urine Na ($r=0.3$, $P<0.0001$) and volume ($r=0.434$, $P<0.0001$) but not with total U-PA activity/GFR. The total U-PA activity correlated with GFR ($r=0.41$, $P<0.0001$) but the total U-PA activity/GFR correlated inversely with the GFR ($r=0.552$, $P<0.0001$). Our result suggests that as the renal mass decreases, the total urine plasminogen activator activity decline, but remnant nephrons produce larger amounts of plasminogen activator activity than do normal nephrons.

Key Words: *Urine Plasminogen Activator, Progressive Renal Failure*

INTRODUCTION

Two-chain urokinase was first isolated from human urine in 1965-1966[1,2]. After this discovery, attention was directed to the potential usefulness of urokinase as a thrombolytic agent in thromboembolic diseases. But little is known about the role of plasminogen activator activity in normal renal physiology. Also, the site of plasminogen activator production is not known, nor is the change in urine fibrinolytic activity with declining renal function. It now seems clear that the glomerulus has an intrinsic mechanism for removing fibrin deposits[3]. In the presence of massive intravascular fibrin deposion, glomerular survival depends upon glomerular fibrinolytic capacity[4]. If this capacity to remove deposited fibrin is insufficient, necrosis results. On the other hand, adequate plasminogen activator activity will remove glomerular fibrin with restoration of glomerular integrity[5]. The amount of plasminogen activator activity produced by remnant nephrons may be linked to the chronicity of renal disease or progression of nenal failure.

A correlation was found between glomerular function as measured by creatinine clearance and urokinase excretion. When the creatinine clearance decreased, the urokinase excretion also decreased regardless of the etiology of kidney disease[6]. Some investigators[7,8] were unable to detect plasminogen activator in the urine of uremia patients. However, it is not known how functional

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nephrons produce the plasminogen activator as the renal function progresses to renal failure. To answer this question, we measured the plasminogen activator activity of urine in patients of various renal function deterioration and attempted to measure the plasminogen activator activity production of remnant nephrons.

METHOD

1. Material

Seventy-three patients, 35 women and 38 men, aged 25 to 75 years, and one 42-year-old healthy male participated in the study.

The serum creatinine concentration was less than 1.5 mg/dl in 41 cases, between 1.6~3.0 mg/dl in 10 cases, between 3.1~6.0 in nine cases and over 6.0 mg/dl in 13 cases. The 24-hour urine protein was less than 250 mg in 24 cases, between 251 mg~1 gm in 16 cases, between 1~3 gm in 15 cases and over 3 gm in 17 cases. The underlying disease were chronic glomerulonephritis (twentyfive cases), diabetes mellitus (seven cases), hypertension (nine cases), cystic disease (two cases) and undermined (ten cases).

2. GFR

Endogenous creatinine clearance was measured in L/day

Fractional Sodium Excretion Rate (FeNa, %)

$$\frac{\text{urine Na} \times V}{\text{Serum Na} \times \text{GFR}} \times 100$$

U-PA activity

The U-PA activity was measured by the fibrin plate method as described previously[9]. In brief, 30 μl of urine was placed on a fibrine plate. The plate was left at room temperature for several minutes to allow absorption of the drop into the fibrin layer and was then incubated at 37℃ for 17 hours. Two perpendicular diameters of each lysed zone were measured in mm^2. The 24-hour urine was collected at 7 a.m. Serum and urine protein, creatinine, Na and K concentrations were meausred by the standard autoanalyzer method. Our preliminary study showed the urine plasminogen activator activity was stable for more than two weeks at room temperature.

Total U-PA activity=U-PA activity (mm^2)×urine volume in ml×10^{-3}

Total U-PA activity/GFR

=Total urine plasminogen activator activity/Ccr.

To see whether there is circadian rhythm of U-PA activity and whether the U-PA activity is under the influence of electrolyte concentration and urine osmolality, 12 consecutive urine samples were collected from a 42-year-old healthy male.

3. Statistics

Data analyses were performed using a Macintosh/PC.

Linear or polynomial regression was used to observe the relationship between continuous independent variables and a continuous dependent variable.

RESULT

The plasminogen activator activity of the 12 consecutive urine samples from a healthy individual showed that the U-PA activity varied with time (Fig. 1), but there was no circadian rhythm. The U-PA activity correlated with the osmolality ($r=0.51$, $P<0.001$) and creatinine ($r=0.56$, $P<0.001$) of the urine (Fig. 2), suggesting that its origin is a proximal nephron and is concentrated at a distal nephron.

1. The Effect of GFR on U-PA Activity

The total U-PA activity was directly related to the GFR ($r=0.41$, $P<0.0001$), and the total U-PA activity/GFR was inversely related to the GFR ($r=0.552$, $P<0.0001$), suggesting that as the renal mass decreases, the U-PA activity declines, but the

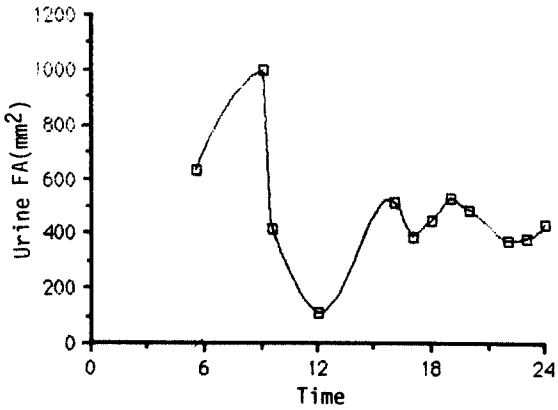

Fig. 1. *Urine plasminogen activator activity of 12 consecutive urine samples during one day from a 42-year-old male subject.*

remnant nephrons produce larger amounts of plasminogen activator activity than do normal nephrons. (Fig. 3a, b)

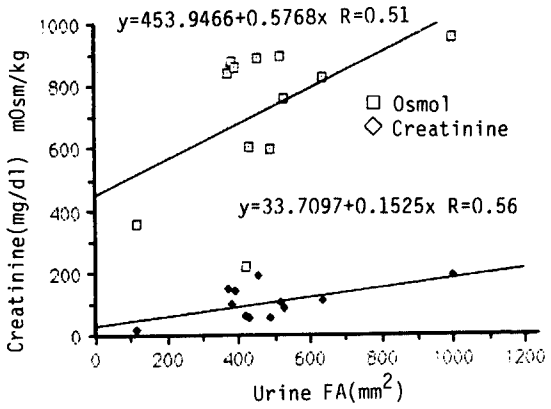

Fig. 2. *The dependence of urine plasminogen activator activity on the urine osmolality and urine creatinine. Urine plasminogen activator activity of 12 consequential urine samples of a 42-year-old candidate during one day, plotted against urine osmolality (mOsm/kg) and urine creatinine concentration (mg/dl).*

2. The Correlation Between GFR and FeNa

The FeNa increased abruptly when GFR decreased below 25 L/day. This pattern was very similar to the relation between total U-PA activity/GFR and GFR (Fig. 3-c).

3. The Effect of FeNa on U-PA Activity

There was no correlation between total U-PA activity and FeNa, but there was a direct correlation between total U-PA activity/GFR and FeNa ($r=0.775$, $P<0.0001$). There was no relationship between 24-hour urine protein and total U-PA activity ($r=0.03$) or total U-PA activity/GFR ($r=0.03$). The total U-PA activity, however, correlated with 24-hour urine Na ($r=0.3$, $P<0.0001$) and volume ($r=0.434$, $P<0.0001$) (Fig. 4-a, b).

DISCUSSION

The purpose of this study was to evaluate the

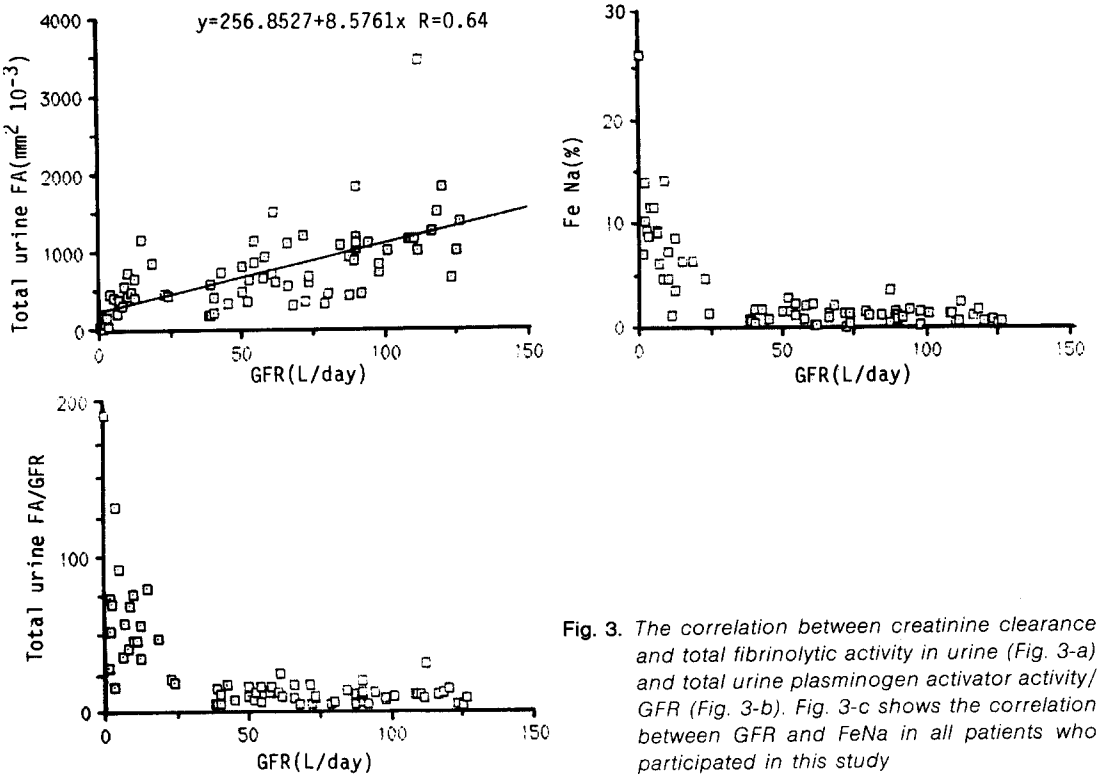

Fig. 3. *The correlation between creatinine clearance and total fibrinolytic activity in urine (Fig. 3-a) and total urine plasminogen activator activity/GFR (Fig. 3-b). Fig. 3-c shows the correlation between GFR and FeNa in all patients who participated in this study*

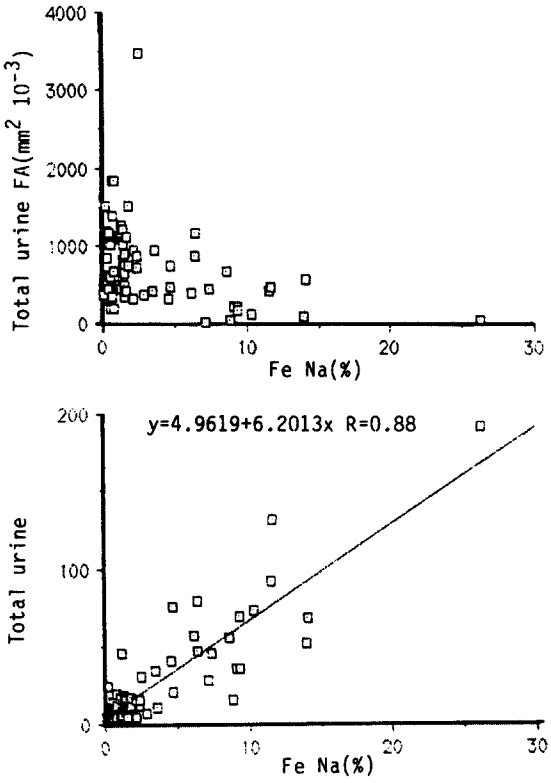

Fig. 4. *The correlation between FeNa (%) and total urine fibrinolytic activity (Fig. 4-a) and total urine plasminogen activator activity/GFR (Fig. 4-b).*

changes in urine plasminogen activator as renal failure progresses. We used the fibrin plate method. It is a simpler and more sensitive method than the fibrin tube method as described by white et al.[2]. Many factors are involved in the pathogenesis and chronicity of renal failure[10], but there is good evidence that fibrin deposition and intravascular coagulation may be destructive to glomeruli[11]. Whatever the primary pathogenetic insult may be, the destructive glomerular process might be mediated in large part by coagulation, fibrin deposition and crescent formations within the glomerulus[12~14]. Even though the precise mechanisms of fibrin deposition and removal are poorly understood, it is generally accepted that glomerulus possesses fibrinoltic activity mediated by the elaboration of a plasminogen activator[3]. Since the plasma plasminogen activator in all probability is produced in the vascular wall[15~17], it seems likely that this is also from the glomerular endothelial cell. In normal circumstances, this activator will then be transported with the glomerular filtrate to the urinary tract. But until now there has been no evidence that glomerular plasminogen activator activity yields U-PA activity or U-PA activity reflects the glomerular plasminogen activator activity. Blood and U-PA activity are generally reported as diminished in glomerulonephritis and in both acute and chronic renal failure[18~22]. In this study, we demonstrated that as the GFR decreases, the U-PA activity concentration and total U-PA activity also decrease. But total urine plasminogen activator activity/GFR increased suddenly when the GFR fell below about 25 L/day. The correlation between total U-PA activity/GFR and GFR was very similar to that of FeNa and GFR. The FeNa also increased abruptly as the GFR fell below 25 L/day. The increment of FeNa is due to the decreased reabsorption of filtered Na. Otherwise the urine plasminogen activator activity is not filtered but is produced in nephron. This increased U-PA excretion by remnant nephrons may be explained as follows: The overloading of solute or GFR itself, which remnant nephrons faced to, might be the stimulant of urine plasminogen activator activity production. Our study does not elucidate the physiologic role of this increased plasminogen activator production of remant nephrons. It is possible that increased urine fibrinolytic activity is necessary for the remnant nephrons to function, but in some situations it may contribute to the progression of renal failure.

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