The role of renin in renal failure associated with hepatic failure

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Summary

A review of the literature has shown that the role of renin in renal failure is not resolved. It has been invoked as an aggravating factor: decreased renal perfusion releasing large quantities of renin sufficient to cause further renal vasoconstriction. If so, then angiotensin generation and action must occur entirely intrarenally since the vasoconstriction appears to be confined entirely to this vascular bed. It may prove necessary to evaluate the renin-angiotensin system within the kidney rather than peripherally. Elevated renin levels in peripheral plasma are at least as likely to be a consequence of reduced renal perfusion as a cause of it.

The few studies so far undertaken of the renin-angiotensin system in renal failure associated with liver disease are inconclusive. If further studies should ascribe a role to renin in the pathology of renal failure, then it may be possible to treat the condition by pharmacological manipulation of the renin-angiotensin system and thereby prevent some of the more serious consequences of renal failure.

Introduction

Acute renal failure may be classified into two main categories: the 'toxic' type, such as that produced by carbon tetrachloride and heavy metals, is associated with extensive tubular damage; and the 'circulatory' type, which is characterized by a profound reduction of renal blood flow but accompanied by few or no histological lesions (Oliver, MacDowell and Tracey, 1951). This implies that a renal vasoconstriction of humoral or neurogenic origin is present in the circulatory type of acute renal failure; the near normal total peripheral resistance often observed in circulatory renal failure suggests the vasoconstriction is confined to the kidney (Lauson, Bradley and Cournaud, 1944).

Both types of renal failure are seen in association with hepatic failure. Renin has been implicated in the development of renal failure; the evidence for this is reviewed. The results of a preliminary study of the role of the renin-angiotensin system in the

pathology of renal failure associated with liver disease are presented.

Renin in renal failure

It has been postulated that the renin-angiotensin system may play a role in circulatory renal failure in man (Brown *et al.*, 1970). These authors noted that the plasma renin concentration was elevated in the early stages of acute renal failure, but fell as the disease progressed. In a subsequent investigation the same group infused glycerol intravenously into rabbits to produce an experimental model of circulatory renal failure (Brown *et al.*, 1972). This procedure produced renal ischaemia and a cessation of glomerular filtration. A rise of plasma renin concentration was also observed, the peak of which preceded the blood urea concentration peak, suggesting that renin may have been responsible, in part, for the renal failure.

The development of glycerol-induced renal failure may be partially prevented by prior sodium loading, a procedure that depletes renal renin (Thiel, McDonald and Oken, 1970; Di Bona and Sawin, 1971), or by passive immunization against angiotensin II (Powell-Jackson *et al.*, 1972). By attenuating the activity of the renin-angiotensin system in either of these ways, the severity of the glycerol-induced renal failure may be reduced. However, the high renin levels are still observed and there is still an initial ischaemic period lasting 4-6 hr. This led Thiel *et al.* (1970) to suggest that there were two phases of ischaemia—the first due to glycerol and the second to renin. It is such evidence that has been used to implicate renin in the pathophysiology of acute renal failure. Renin may have a role in the pathogenesis of circulatory renal failure by the generation of angiotensin I and its subsequent conversion within the kidney to angiotensin II, which could then act directly on the renal vasculature without entering the systemic circulation (Thurau *et al.*, 1967). This hypothesis requires the presence of converting enzyme intrarenally to convert angiotensin I, the product of the action of renin upon renin-substrate,

to the active octapeptide angiotensin II. The evidence currently available from animal studies suggests that the conversion of angiotensin I to II does occur within the kidney but at a low rate (Hofbauer *et al.*, 1973; Leckie *et al.*, 1972; Merrill, Peach and Gilmore, 1973).

An observation that may resolve this difficulty was made by Carrière and Biron in 1970. They found angiotensin I had 5% of the vasoconstrictor potency of angiotensin II. If a sufficiently high angiotensin I generation rate existed within the kidney as a result of the high renin levels there, it may be sufficient to produce a local vasoconstriction *per se*.

Little is known of the action of renin intrarenally, but if renal blood flow is markedly reduced it is probable that renin is released in large quantities into the extracellular fluid and a high angiotensin I generation may be expected to ensue. High levels of renin and angiotensin I intrarenally would result both from their high production rates and their impaired removal from the kidney. If the levels of either angiotensin I or II within the kidney were sufficient to produce a local vasoconstriction in spite of the action of tissue angiotensinases, then they could reasonably be ascribed the role of selective renal vasoconstrictors.

However, it remains to be proved that the suppression of renin was responsible for the protection from glycerol-induced renal failure. A close examination of the relationship between the severity of renal impairment and plasma renin activity (PRA) in the rat was undertaken by Matthews, Morgan and Johnston (1974). They found that only mercury-induced renal failure induced a rise of PRA; renal failure induced by intramuscular glycerol produced a significant drop in PRA. In neither case were the authors able to correlate the progress of the renal failure with changes in the renin-angiotensin system. Furthermore, immunization against angiotensin II was ineffective in preventing the renal failure in their study.

Glycerol-induced renal failure can be extremely variable, and perhaps the results obtained with this model should be viewed more circumspectly. In addition, the condition met with in clinical practice may bear little relationship to the glycerol model because of the varying aetiologies of human renal failure. Indeed, a rise of plasma renin is occasionally observed in patients recovering from renal failure (Kokot and Kuska, 1969).

The renin-angiotensin system in liver disease

Abnormalities of the renin-angiotensin system are commonly found in association with liver disease. PRA may be normal or elevated depending on the degree of associated renal impairment (Barnardo *et al.*, 1970). Renin substrate concentrations (an α_2 -

globulin of hepatic origin) are predictably low (Schroeder *et al.*, 1970). The infusion of dopamine into patients with cirrhosis with varying degrees of renal impairment has demonstrated a reciprocal relationship between effective renal plasma flow (as measured by PAH clearance) and PRA (Barnardo *et al.*, 1970). The increased renal plasma flow resulting from the infusions of dopamine reversed the elevated PRA. This suggests that PRA is determined, at least in part, by the renal blood flow, which accords with current theories of the control of renin release.

The possible significance of renin-substrate depletion in liver disease

Berkowitz, Galvin and Miller (1974) have suggested a completely different approach to the role of the renin-angiotensin system in renal failure associated with liver disease. On the basis of isolated perfused kidney experiments they have suggested that intrarenally generated angiotensin acts upon the renal vasculature in such a way as to redirect blood flow towards the cortex. Thus, renin-substrate depletion might lead to a reduction in intrarenal generation of angiotensin and a reduction in renal cortical perfusion. This may be restored by renin-substrate infusion. An examination of their data, however, shows that the renin-substrate depletion that occurs during the course of the perfusion experiment is accompanied by an enormous increase in renin concentration, so that angiotensin generation would be expected to rise despite the fall in renin-substrate levels. Isolated perfused kidneys generally lose much of their functional ability, consequently, great caution should be exercised in interpreting data obtained in such preparations.

Renin-substrate infusion (Berkowitz, Miller and Rosato, 1974) or liver transplantation (Iwatsuki *et al.*, 1973) into patients with liver disease have been reported to ameliorate the accompanying circulatory renal failure. However, it would seem premature to ascribe the improvement in renal function to the repletion of renin-substrate since it could be due to some other consequence of the restoration of hepatic function.

Preliminary results of a study of the renin-angiotensin system in liver disease

Two patients with fulminant hepatic failure and acute renal failure associated with acute tubular necrosis were studied. PRA and renin-substrate levels were estimated in peripheral arterial plasma and in renal venous plasma. In this study PRA is equated to the angiotensin I generation rate under standard conditions, without added substrate. The generated angiotensin I was estimated by radioimmunoassay. The results are shown in Table 1.

An arteriovenous difference of PRA could not be

demonstrated in either case. However, the first patient showed evidence of renin-substrate consumption within the kidney. This degree of substrate consumption would produce about 115 ng/ml of angiotensin I. Angiotensinase action would markedly reduce the level of this peptide which has only one-twentieth of the vasoconstrictor potency of angiotensin II. However, it is possible that it may cause some vasoconstriction because the normal plasma levels of angiotensin II (20–100 pg/ml) are probably only just sub-pressor.

TABLE 1. Plasma renin activity and substrate concentration in two patients with renal and hepatic failure. Three determinations were performed on each plasma sample. The data are expressed as the mean $\pm$ 1 standard deviation

Patient	PRA ng/ml/hr		Renin-substrate ng/ml	
	Artery	Renal vein	Artery	Renal vein
1	3.24 $\pm$ 0.26	3.47 $\pm$ 0.06	479 $\pm$ 25	364 $\pm$ 48
2	1.34 $\pm$ 0.25	1.56 $\pm$ 0.13	881 $\pm$ 33	936 $\pm$ 69

Discussion

Schroeder *et al.* (1970) reported a number of cases of circulatory renal failure with cirrhosis. In every case peripheral venous plasma renin concentration was markedly elevated. In two cases the arteriovenous difference of plasma renin across the kidney was estimated, but in only one was there evidence of renin secretion: in the other the data suggested that renin was being removed from the plasma by the kidney.

Taking these four cases together, there appears to be no consistent pattern emerging. In future studies it would be of benefit to estimate the Michaelis Constant and the plasma renin concentration as well as substrate and PRA in both arterial and renal venous plasma. It may then be possible to elucidate the true status of renin in this pathological condition.

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