The role of renin in renal failure associated with hepatic failure

I. K. SMITH
B.Sc., Ph.D.

Department of Biochemical Pharmacology, King's College Hospital Medical School, Denmark Hill, London S.E.5

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 Gil-
more, 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 sup-
pression of renin was responsible for the protection
from glycerol-induced renal failure. A close examina-
tion 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 addi-
tion, 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 α₂-
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 sug-
gested a completely different approach to the role of
the renin-angiotensin system in renal failure associ-
ated with liver disease. On the basis of isolated per-
 fused 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 per-
fusion. 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 con-
centration, 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
care 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 radio-
immunoassay. 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 ± 1 standard deviation.

<table>
<thead>
<tr>
<th>Patient</th>
<th>PRA ng/ml/hr</th>
<th>Renin-substrate ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Artery</td>
<td>Renal vein</td>
</tr>
<tr>
<td>1</td>
<td>3.24 ± 0.26</td>
<td>3.47 ± 0.06</td>
</tr>
<tr>
<td>2</td>
<td>1.34 ± 0.25</td>
<td>1.56 ± 0.13</td>
</tr>
</tbody>
</table>

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.

References


The role of renin in renal failure associated with hepatic failure
I. K. Smith

Postgrad Med J 1975 51: 506-508
doi: 10.1136/pgmj.51.598.506

Updated information and services can be found at:
http://pmj.bmj.com/content/51/598/506

These include:

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/