Arterial wall or plasma renin in hypertension?

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Introduction

Secretion of renin by the kidney is one of the mechanisms by which blood pressure is maintained when the circulation is threatened by extracellular fluid depletion or haemorrhage. Renin does not act directly upon the cardiovascular system, but exerts an indirect pressor effect through the production of the octapeptide hormone, angiotensin II, which is formed by the hydrolysis of the decapeptide angiotensin I under the influence of converting enzyme. Angiotensin I is in turn produced by the action of renin upon an α-globulin substrate secreted by the liver (for review and references, see Peach, 1977).

Elevation of plasma angiotensin II, even within the normal range, raises blood pressure (Chinn & Dusterdieck, 1972), suggesting that the renin-angiotensin system has a role in the physiological control of blood pressure. The part played by this system in hypertension caused by renal ischaemia is more controversial. Plasma renin values may be normal in clinical renovascular hypertension (Peart, 1975) and in some models of experimental renovascular hypertension (e.g. Koletsky & Rivera-Velez, 1970; Miksche, Miksche & Gross, 1970).

The belief that renin must in some way still be involved in the development of renovascular hypertension has produced several attempts to explain how renin can be important despite normal plasma renin values. These include the hypotheses that:

(1) Renin initially causes a rise in blood pressure, which is then maintained by structural changes induced in the peripheral resistance vessels by the increased load. The importance of such changes has been well demonstrated in spontaneously hypertensive rats (probably a non-renin-dependent model), although there is less evidence for such a mechanism in renovascular hypertension (Folkow, Hallbäck, Lundgren, Sivertsson & Weiss, 1973).

(2) Although renin values are apparently normal, they are ‘inappropriately high’ for the state of sodium balance (e.g. Schalekamp, Beevers, Briggs, Brown, Davies, Fraser, Lebel, Lever, Medina, Morton, Robertson & Tree, 1973).

(3) In addition to the well-described immediate pressor effect of renin or angiotensin, there is a slow mechanism (Brown, Davies, Morton, Robertson, Cuesta, Lever, Padfield, Trust, Bianchi & Schalekamp, 1976), perhaps mediated by hypersensitivity to normally sub-pressor doses of angiotensin II (Dickinson & Lawrence, 1963).

(4) Renin may act as a local tissue hormone, so that circulating concentrations of renin or angiotensin II may not reflect the concentration of these substances at the receptor site. There would thus be an analogy with catecholamines and perhaps prostaglandins (McGiff & Vane, 1975). Particular interest has been shown in two tissues: the central nervous system and the blood vessel wall. Although renin is probably formed locally within the central nervous system (Ganten, Schelling, Vecsei & Ganten, 1976), its role, if any, at this site is...
debatable (Reid, 1977). The purpose of the present review is to describe the evidence for, and examine the possible roles of, vascular renin.

**Arterial wall renin**

In all studies, the tissue analysed has been aorta or large artery and the unverifiable assumption has been made that the renin content of this tissue reflects renin concentration in the more distal parts of the arterial tree, which maintain peripheral resistance. Early studies showed that an extract of arterial wall contained an enzyme which released pressor material from plasma (Jimenez-Diaz, Barreda & de la y Molina, 1947; Dengler, 1956). Later kinetic studies of hog (Gould, Skeggs & Kahn, 1964) and rat aortic extracts (Barrett, Eggema & Sambhi, 1978) indicated that enzymatic activity resulting in the generation of angiotensin was indistinguishable from that of renal renin. The specificity of the enzyme is extremely important in evaluating its physiological role. Almost every tissue studied contains enzymes, which, when incubated *in vitro* with renin substrate, will yield angiotensin. Some of these are undoubtedly acid proteinases with a pH optimum well below that of renin, and which probably play no role in angiotensin generation *in vivo* (Thurston, Bing, Hurst & Swales, 1978). Even at a physiological pH it cannot be assumed that, because an enzyme is present, it performs the expected physiological role. For instance, the enzyme 'pseudo-renin' extracted from the submaxillary gland hydrolysates synthetic (tetradecapeptide) substrate, but is inactive against plasma substrate (Skeggs, Levine, Lentz, Kahn & Dorer, 1977).

The first prerequisite for biological activity is the presence of renin substrate and converting enzyme, in addition to renin in the blood vessel wall. Little is known of renin substrate at this site, although it would be expected that substrate and renin derived from the plasma would have access to the same tissue sites. There is good evidence that conversion of angiotensin I into angiotensin II can take place in the peripheral vascular bed of dogs (Aiken & Vane, 1972), sheep (Osborn, Tildesley, O'Gorman & Mahler, 1971) and in the forearm vessels of man (Collier & Robinson, 1974).

**Changes in vascular renin**

Rat aortic renin-like activity has been observed to rise with procedures that elevate plasma renin and to fall after bilateral nephrectomy (Rosenthal, Boucher, Rojo-Ortega & Genest, 1969). By contrast, in other studies in dogs, arterial renin failed to fall over 12 days after bilateral nephrectomy (Hayduk, Ganten, Boucher & Genest, 1972). A low incubation pH was used in these studies and it is uncertain, therefore, how far acid proteinase and how far renin was being assayed. Basso & Taquini (1971) also demonstrated sustained vascular renin in dogs after bilateral nephrectomy: in these studies, specimens were acidified to pH 1.6, a procedure which may result in the formation of active renin from inactive material (Leckie, 1973). The incubation pH appears critical in such studies. Rat aortic renin measured at pH 6.5 rose with salt depletion and fell with salt loading and bilateral nephrectomy; measured at pH 5.3, no consistent changes could be detected (Thurston et al., 1978).

**Role of vascular renin**

Such changes in vascular renin could be secondary to alterations in plasma renin and of no physiological relevance. To demonstrate a physiological role for vascular renin, it is necessary to demonstrate activity *in vivo*, which can only be attributed to renin contained within the blood vessel wall. The major difficulty in such an approach lies in distinguishing between the role played by plasma renin and that played by vascular renin. Where both change in parallel, such a distinction becomes well-nigh impossible. The renin–angiotensin system contributes to two phenomena which have proved useful in delineating a function for vascular as opposed to plasma renin. These two phenomena are: the maintenance of hypertension due to renal ischaemia with the opposite kidney *in situ* (Goldblatt two-kidney hypertension) and alterations in vascular responsiveness to angiotensin II. The presence of elevated plasma renin concentrations and the fall in blood pressure produced by renin–angiotensin system blockade both suggest that renin plays some role in the early phases of hypertension produced by renal artery constriction, so long as the opposite kidney remains intact (Davis, 1977).

The pressor response to injections of angiotensin II is closely related to plasma renin and angiotensin II concentrations. Where plasma renin is high (as, for instance, in salt depletion), the pressor response to angiotensin II is low, whereas when plasma renin is reduced (as in salt loading or after bilateral nephrectomy) pressor sensitivity to angiotensin II is increased (Samwer, Schreiber, Molzahn & Oelkers, 1974). By inhibiting the
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generation of angiotensin II with converting enzyme blockade, it is possible to increase sensitivity to angiotensin II injections. Pressor responsiveness thus appears to be modulated by the number of unoccupied vascular receptors available to respond to the exogenous angiotensin (Thurston & Laragh, 1975). Change in the total number of receptors does not appear to be as important, if, indeed, it plays any role at all, in these situations (Thurston, 1976). The pressor response to angiotensin II reflects, therefore, partly at least, the local concentration of angiotensin II at the receptor site (Fig. 1).

Angiotensin antibody paradox

The preparation of specific angiotensin II antisera offered a potential tool for investigating the role of the renin–angiotensin system in blood pressure control. The results were unexpected in two ways. First, in the majority of studies, the effect of antiserum upon blood pressure was small or nonexistent even in forms of hypertension (such as the Goldblatt two-kidney model) where the renin–angiotensin system was believed to play some role (Hedwall, 1968; Oates, Stokes, Storey, Glover & Snow, 1974; Thurston & Swales, 1974a). The second anomaly was first pointed out by Brunner, Chang, Wallach, Sealey & Laragh (1972). A larger volume of antiserum was required to block the pressor response to angiotensin II when circulating concentrations of angiotensin II were low (i.e. after salt loading or bilateral nephrectomy) than when such values were high (i.e. after salt depletion). Clearly this was precisely the opposite result to that which would be predicted if the major determining factor for antiserum volume was the amount of angiotensin II available for binding. Brunner et al. (1972) suggested that vascular receptors and antibody competed with each other for free angiotensin and that increased receptor ‘avidity’ produced by salt loading or nephrectomy increased the blocking volume of antiserum. Such sodium-related changes in angiotensin receptors have not been demonstrated (Devynek & Meyer, 1976; Thurston, 1976; Devynck, Pernollet, Macdonald, Matthews, Raisman & Meyer, 1978), and in any case it seems intrinsically unlikely that receptor avidity should be increased when the pressor action of angiotensin is unimportant (after salt loading), yet decreased when the pressor action of angiotensin II fulfils an important physiological role (after salt depletion).

Vascular renin hypothesis

Another hypothesis has been put forward to explain both the ineffectiveness of antiserum in lowering blood pressure, and the anomalous antiserum blocking requirements. According to this hypothesis, vasoconstrictor angiotensin II is generated at a site within the blood vessel wall, and this site is not accessible to the antibody molecules within the duration of the experimental studies (Swales & Thurston, 1973; Swales, Tange & Thurston, 1975). A similar suggestion had previously been made by Daum, Uehleke & Klaus (1966) to explain some analogous phenomena with aminopeptidase, which rapidly degrades angiotensin II. Infusion of aminopeptidase was much more effective in impairing the pressor response to angiotensin II than in impairing the pressor response to renin. It was concluded that angiotensin II generated by renin within the blood vessel wall was less accessible to aminopeptidase than was circulating angiotensin II.

A similar pattern of results has been obtained with angiotensin II antisera. Small amounts of this material are highly effective in blocking the pressor response to angiotensin II and in restoring to normal blood pressure which has been elevated by angiotensin infusion (Swales, 1976). On the other hand, the pressor response to renin is only partially reduced in antibody-pretreated rats, and hypertension produced by renin infusion is resistant to

![Fig. 1. Pressor response to exogenous angiotensin (A) is small when vascular receptors are occupied by endogenous angiotensin (cross-hatched circles in a). Responsiveness is much greater when receptors are unoccupied (b).](image-url)
angiotensin antiserum injection. By contrast, angio-
tensin blockade with the competitive antagonist
saralasin is much more effective in reducing hyper-
tension produced by renin infusion (Bing &
Nielson, 1973; Thurston & Swales, 1974b) and in
Goldblatt two-kidney hypertension (Thurston &
Swales, 1974a). Local generation of angiotensin at
a site which is not immediately accessible to
antibody would also explain the need to give larger
quantities of antiserum to block the angiotensin II
pressor response when plasma renin is low. If most
vascular angiotensin receptors are unoccupied, a
pressor response will be produced by very small
plasma concentrations of angiotensin; the amount
of antiserum needed to reduce plasma concen-
tration below this therefore will be much higher
than when few receptors are free (Swales et al.,
1975).

The interpretation of antiserum experiments is
clearly more complex than was originally expected.
Oster, Bauknecht & Hackenthal (1975) suggested
that enough free angiotensin was present to
maintain blood pressure even in the presence of
excess antibody. Although this neither explains the
correction of angiotensin infusion hypertension by
antiserum, nor the analogous effects of amino-
peptidase infusion, it does indicate the need for a
fresh approach in analysing the role of vascular
renin.

**Vascular renin after nephrectomy**

One situation where the actions of vascular and
plasma renin might be distinguished is after
bilateral nephrectomy (Rosenthal et al., 1969;
Hayduk et al., 1972). There is indirect evidence
that the persistence of vascular renin is much more
prolonged than that of plasma renin. Thus Schaect-
telin, Regoli & Gross (1964) observed the effect of
injecting renin into one member of a pair of
nephrectomized rats in which the circulations could
be made to intercommunicate. The blood pressure
of the injected rat was still elevated when no
circulating renin could be detected by opening up
the communication between the two circulations
and monitoring the blood pressure in the second
rat. Pressor responsiveness to angiotensin II in-
usions, which, as we have seen, is partly at least
determined by endogenous renin, changes much
more slowly than does plasma renin when rats are
bilaterally nephrectomized. The volume of angio-
tensin II antiserum needed to block the pressor
response to a given dose of angiotensin also
changes at a similar low rate (Swales et al., 1975).

If vascular renin has a longer half-life than
plasma renin, it should be possible to study the
relative roles of renin at these two sites by per-
forming bilateral nephrectomy upon a model of
hypertension where renin appears to be of impor-
tance (e.g. Goldblatt two-kidney hypertension).
Aortic renin-like activity, measured at an in-
cubation pH 6.5, remains elevated in such animals
for several hours; only at 6 h and beyond is aortic
renin substantially reduced (Thurston et al., 1978).
Plasma renin, on the other hand, has a relatively
short half-life (10–15 min). This slow decline in
vascular renin-like activity is paralleled by an
equally slow decline in the depressor response to
blockade of the renin–angiotensin system
(Thurston & Swales, 1977). Thus vascular, rather
than plasma, renin appears to be the important
controlling factor in blood pressure elevation in this
model.

Selective uptake of renin from plasma by
vascular tissue theoretically offers a mechanism by
which the renin–angiotensin system could maintain
blood pressure even when plasma renin con-
centrations are not elevated. Such a divergence
between plasma and aortic renin has recently been
observed in spontaneously hypertensive rats
treated with hydralazine or a diuretic (Barrett
et al., 1978). There is no relevant clinical evidence in
man. Indirect evidence suggests that plasma renin
usually reflects the degree to which the renin–
angiotensin system is maintaining blood pressure.
Thus there is usually a close relationship
between the blood pressure fall induced by renin–angio-
tensin blockade and plasma renin or angiotensin II
values (e.g. Streten, Anderson, Freiberg &
Dalakos, 1975; Case, Wallace, Keim, Weber,
Drayer, White, Sealey & Laragh, 1976; McGrath
& Ledingham, 1978). This would therefore indicate
that vascular and plasma renin are usually related
during steady-state conditions in man. Whether a
closer relationship would be observed between
arterial renin concentrations and the response to
blockade is unknown, but at present there is no
convincing evidence that vascular renin maintains
blood pressure independently of plasma renin for
prolonged periods in man.

**Conclusions**

Local generation of angiotensin II by renin-like
activity within the resistance vessel walls is impor-
tant both in maintaining blood pressure and in
determining pressor sensitivity to exogenous angio-
tensin. Such renin-like activity is biochemically
similar to, if not identical with, renal renin and is probably derived from the kidney. It has a much longer half-life than plasma renin. The renin–angiotensin system thus probably functions as a local humoral control system within the blood vessel wall.

References


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