Agents Which Block the Action of the Renin-Angiotensin System

By James O. Davis, Ronald H. Freeman, J. Alan Johnson, and William S. Spielman

The role of the renin-angiotensin system in the control of arterial blood pressure and aldosterone secretion has been studied extensively in homeostasis, hypertensive disease, and edematous states. For many years it has been realized that the availability of effective blocking agents for renin or for angiotensin II might help greatly in the study of this system and might have important value in the treatment of conditions such as renal hypertension and heart failure. During the past few years, an increasing number of blocking agents for the renin-angiotensin system have been developed. These agents act at one of three sites: (1) they block the action of renin in plasma, (2) they prevent converting enzyme from forming angiotensin II from angiotensin I, or (3) they block the receptor sites for angiotensin II in arteriolar smooth muscle and adrenal cortex. In addition, adrenergic blocking agents such as propranolol decrease the release of renin from the renal juxtaglomerular cells. This review is concerned only with the agents which block the action of the renin-angiotensin system, not with those that decrease the release of renin.

The new observations with blocking agents have helped solve several specific problems under investigation, and, in addition, new important functions of the renin-angiotensin system have been uncovered. For example, it is now recognized (1-5) that in low output states angiotensin II acts directly on the peripheral arterioles including the renal vasculature to increase peripheral resistance, decrease renal blood flow, and maintain arterial blood pressure. In this review, the recent findings have been collated to present this new knowledge on the physiology of angiotensin II, to evaluate the present state of our knowledge on such important problems as the pathogenesis of experimental renal hypertension, and to stimulate additional research on the physiology of the renin-angiotensin system.

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angiotensin II function. Insertion of sarcosine in the 1 position has increased the in vivo potency of the 8-Ile-analogue (18), and, presumably, other analogues such as 1-Sar-8-Ala-angiotensin II are more potent in vivo because of the sarcosine substitution. Two explanations have been offered for this influence of sarcosine (17, 18). It has been suggested that sarcosine protects the molecule from enzymatic degradation and prolongs the biological half-life and that sarcosine increases the binding affinity of the analogue for the receptor site. One of the enzymes that inactivates angiotensin II is an aminopeptidase which acts on the NH$_2$-terminal amino acid; replacement of this terminal amino acid with sarcosine apparently prevents this enzymatic action. It should be remembered that actions other than the specific antagonistic ones have been demonstrated for some of the analogues. For example, some 8-substituted derivatives of angiotensin II have been reported to release catecholamines from the adrenal medulla (19). These considerations emphasize the need for additional study to define more completely the pharmacology of these analogues.

THE RENIN-ANGIOTENSIN SYSTEM IN LOW OUTPUT STATES WITH HYPERALDOSTERONISM

One of the most important new findings from observations with the angiotensin II antagonists is that angiotensin II is a primary controller of arterial blood pressure in low cardiac output states. In sodium-depleted dogs and in dogs with thoracic caval constriction, 1-Sar-8-Ala-angiotensin II produces a fall in arterial blood pressure (1-5), whereas arterial blood pressure is unchanged by this antagonist in normal dogs. The same response of the peripheral arterioles to 1-Sar-8-Ala-angiotensin II occurs in sodium-depleted rats (20, 21). Moreover, in a recent preliminary report (22), it has been found that a nonapeptide converting enzyme inhibitor reduces blood pressure when angiotensin II formation is blocked in sodium-depleted and in adrenalectomized dogs with an initially low arterial blood pressure. Thus, observations with these blocking agents have revealed an important and previously uncovered role for angiotensin II in the maintenance of arterial blood pressure in low output states; it seems likely that angiotensin II acts on specific receptor sites in smooth muscle of the peripheral arterioles to effect an increase in peripheral resistance. It appears, therefore, that the development of low cardiac output leads to increased activity of the renin-angiotensin system and that increased angiotensin II is an important compensatory factor acting to maintain arterial blood pressure within normal limits. An interesting incidental realization (2, 4) from this experiment is that the decreased pressor response to exogenous angiotensin II in animals (23) or patients (24) with high plasma levels of angiotensin II now seems explicable; it appears likely that available arteriolar smooth muscle receptor sites are sufficiently saturated with endogenous angiotensin in secondary aldosteronism with hyperangiotensinemia that exogenously injected octapeptide is less effective.

To study the role of angiotensin II in the control of body fluid volume, the effects of 1-Sar-8-Ala-angiotensin II on steroid secretion have been observed in sodium-depleted dogs (2, 4) and in dogs with thoracic caval constriction (1-4). It is well-known that the renin-angiotensin system is important in the control of aldosterone secretion, but the relative importance of this control mechanism varies among species especially during sodium depletion (25). Thus, this angiotensin II analogue has been used to study the importance of angiotensin II in the control of aldosterone secretion in the dog. The high rates of aldosterone secretion characteristic of sodium depletion and caval constriction fell markedly in both sodium-depleted dogs and dogs with thoracic caval constriction. These data and those on arterial blood pressure in these two experimental states with hyperreninemia and hyperaldosteronism demonstrate an important action for angiotensin II on receptor sites in smooth muscle and adrenal cortex; increased angiotensin II produce effective, important compensatory maintenance of a normal or near normal level of arterial blood pressure in these low output states. These observations, therefore, support the concept of a renin-angiotensin-aldosterone system in the regulation of blood volume and thus, indirectly, in the control of blood pressure (26).

In the studies of steroid secretion in dogs with experimental hyperaldosteronism (1-4), infusion of 1-Sar-8-Ala-angiotensin II increased adrenal blood flow. This finding called attention to the possibility that angiotensin II might control renal blood flow; this possibility has now been verified. When Freeman et al. (5) infused 1-Sar-8-Ala-angiotensin II into the renal artery of dogs with sodium depletion or caval constriction, an increase in renal blood flow occurred. In control experiments on normal dogs, the angiotensin II analogue failed to influence renal blood flow. These findings indicate that
angiotension II acts directly on the renal arterioles in these two experimental situations and decreases renal blood flow; this action is part of the compensatory response to maintain arterial blood pressure in the presence of decreased cardiac output.

An incidental unexpected result from the studies of steroid secretion is the finding that 1-Sar-8-Ala-angiotension II also lowers cortisol secretion in dogs with sodium depletion or caval constriction (1-4). Since cortisol is secreted by the two inner zones of the adrenal cortex, this observation suggests the presence of angiotension II receptors in the zona fasciculata and the zona reticularis. This finding agrees with an earlier report by Peytremann et al. (27), who observed an increase in corticosteroid production during incubation of zona fasciculata cells from bovine tissue with angiotension II.

From the early studies in the domestic white rat, the mechanisms controlling aldosterone secretion during sodium depletion appear to differ from those present in other mammals including man, dog, sheep, rabbits, and even a very primitive mammal, the American opossum. By administration of the nonapeptide converting enzyme inhibitor to sodium-depleted hypophysectomized rats, Spielman and Davis (unpublished observations) have demonstrated a striking drop in aldosterone secretion with an associated fall in arterial blood pressure. However, functional differences in angiotension II receptors have also been demonstrated from in vitro studies of rat zona glomerulosa cells and vascular smooth muscle of rabbit aortic strips (15). Furthermore, the analogue 1-Sar-8-Ile-angiotension II has been used to block the action of angiotension II and the heptapeptide 1-des-Asp-angiotension II on aldosterone biosynthesis in an in vitro system of rabbit adrenal cortex (28). The dose of the analogue required to block the heptapeptide is 25 times greater than that required to block angiotension II, a finding consistent with a higher affinity of the angiotension II receptor for the heptapeptide than for the octapeptide. The heptapeptide is equal in potency to angiotension II in the synthesis of aldosterone in this in vitro system of rabbit adrenal cortex (28) but is 3-5 times as potent in cat adrenal cell suspensions (29). It has also been reported from in vitro studies (30) that angiotension II is bound to a specific membrane receptor in adrenal cortex cells and that angiotension II activates adenylate cyclase in adrenal homogenates. The competitive antagonist 1-Sar-8-Ala-angiotension II inhibits binding of angiotension II by the receptor but does not stimulate adenylate cyclase (30). These studies emphasize one of the important frontiers in research on the function of angiotension II and point to the need for definition of angiotension II receptors at the biochemical level.

1-Sar-8-Ala-angiotension II also produces a striking increase in plasma renin activity in dogs depleted of sodium or with caval constriction (1-4). A similar response in plasma renin activity to this angiotension II antagonist has been reported in both normal and adrenalectomized rats (31). It seems likely that the angiotension II antagonist blocks the normal short-loop negative feedback mechanism of angiotension II which decreases renin release (32). The earlier finding of Miller et al. (33) that plasma renin activity increases more following renal artery constriction in dogs after injection of a nonapeptide converting enzyme inhibitor than it does in untreated dogs after renal artery constriction now seems explicable on the basis of removal of the negative feedback influence of angiotension II. Moreover, the recent observation that this converting enzyme inhibitor increases plasma renin activity in sodium-depleted and in adrenalectomized dogs (22) is also explicable in this manner.

THE RENIN-ANGIOTENSIN SYSTEM IN EXPERIMENTAL RENAL HYPERTENSION

One of the major unresolved problems in the pathophysiology of angiotension is the role of the renin-angiotension system in the pathogenesis of renal hypertension. The blocking agents have been very useful in the study of this problem. The first observations (34, 35) involved the immunization of chronic renal hypertensive dogs with preparations of renin. There was a striking inverse correlation between the development of an antirenin titer in plasma and a fall in arterial blood pressure. Also, passive transfer of plasma containing renin antibodies produced a fall in arterial blood pressure (34). These early studies have been repeatedly criticized, because the renin preparations were crude and could have contained other agents.

A recent surge of interest has occurred in the use of immunization with angiotension II to produce antibodies which might block the action of the octapeptide. This interest began in 1969 with the report of Christlieb et al. (36) that arterial blood pressure falls following immunization of renal hypertensive rats and that the response occurs most frequently in those rats with elevated antibody titers. However, subsequent studies in rats (37) and rabbits (38-40) have failed to confirm this finding and, collectively, the evidence from several laboratories indicates that immunization with
angiotensin II fails to prevent the development or the maintenance of chronic renal hypertension. Also, it has recently been realized (41) that adequate neutralization of angiotensin II by the presence of circulating antibodies does not exclude a role for angiotensin II in the pathogenesis of renal hypertension. Walker et al. (41) have reported that the level of free (unbound) angiotensin II is adequate for angiotensin II to participate in physiological processes despite high titers of antibodies for the octapeptide. It is also possible that angiotensin II has more affinity for the vascular receptor sites than it has for the antibodies. These realizations point to the need for the use and study of specific inhibitors of the renin-angiotensin system.

One of the first inhibitors of renin to be used was the so-called phospholipid renin preinhibitor developed by Sen et al. (42, 43); the phospholipid preinhibitor is the precursor of an active lysophospholipid formed by the action of phospholipase A. The preinhibitor has been found in human, dog, and rat blood. Injection of the preinhibitor reduces the blood pressure in both short-term and long-term (40 weeks duration) renal hypertensive animals. This hypotensive action has been observed in both one-kidney (one renal artery constricted and the contralateral kidney intact) and two-kidney (one renal artery constricted and the contralateral kidney removed) hypertensive rats. However, the blood pressure never returns to normotensive levels, and plasma renin activity is not completely inhibited.

The most extensive attempts to block the renin-angiotensin system and, thereby, to drop arterial blood pressure in experimental renal hypertension have been made with the synthetic analogues of angiotensin II. The experiments of Pals et al. (9, 10) with 1-Sar-8-Ala-angiotensin II provide the basic information and the fundamental background data to show the usefulness of the competitive antagonists of angiotensin II in the study of hypertension. Pals and co-workers (10) found that infusions of this analogue (5–10 μg/kg min⁻¹) reduce arterial blood pressure in conscious rats in the acute phase of unilateral renal hypertension (less than 2 weeks) but are ineffective during the chronic phase of such hypertension (2–5 weeks). As a control experiment, these investigators used conscious normotensive, spontaneously hypertensive and metacorticoid hypertensive rats, but no change in blood pressure occurred in these animals.

At essentially the same time, Brunner et al. (44) studied chronic renal hypertension of 6 weeks duration in both one-kidney and two-kidney rats. They used the same analogue of angiotensin II as did Pals and his associates; in addition, they injected other groups of animals with antisera from rabbits immunized against angiotensin II. Both the 1-Sar-8-Ala-angiotensin II and the antisera reduce arterial blood pressure in the two-kidney but not in the one-kidney renal hypertensive rats. This finding confirms the earlier findings of Bing and Poulsen (45) in two-kidney renal hypertensive rats with the use of antisera. These observations are consistent with earlier reports of normal values for plasma renin activity in chronic one-kidney hypertension and elevated plasma renin activity in chronic two-kidney hypertension.

More recently, both Bing and Nielsen (46) and Bumpus et al. (17) have found that specific competitive antagonists reduce arterial blood pressure in rats with one-kidney renal hypertension of 2–2.5 months (46) and of 4–6 weeks duration (17), but in a preliminary experiment on three rats with chronic one-kidney hypertension of more than 30 weeks duration Bumpus et al. (17) have reported that 8-Ile-angiotensin II fails to reduce arterial blood pressure. In two-kidney hypertension, both groups (17, 46) have observed a drop in arterial blood pressure in chronic hypertensive rats; the animals of Bumpus et al. (17) were hypertensive for only 6 weeks. In these observations of renal hypertension in rats, normal animals were studied as controls (17, 44–46). The results from different groups (17, 44–46) are in agreement that a hypotensive response to these angiotensin II antagonists in normal animals occurs only but not always in anesthetized rats and not in conscious normal animals.

Thus, the results appear to be consistent in that rats with chronic two-kidney hypertension respond to competitive antagonists with a fall in arterial blood pressure. On the contrary, more work is needed to clarify the role of the renin-angiotensin system in chronic one-kidney hypertension in the rat; Gavras et al. (21) have reinvestigated the problem. They have found a decrease in arterial blood pressure in response to 1-Sar-8-Ala-angiotensin II in chronic one-kidney hypertensive rats when the animals are sodium-depleted and there is increased activity of the renin-angiotensin system. Their interpretation is that hypertension in the rat is dependent on the state of body fluid volume and that the one-kidney model responds to the angiotensin II analogue because the animals are volume depleted. The sodium-depleted hypertensive
animal is an interesting model and further study might provide new insight into the pathogenesis of renal hypertension.

A group of peptides from Bothrops jararaca venom inhibits the converting enzyme and, thus, blocks the conversion of angiotensin I to angiotensin II (47). Several of these peptides have been isolated, characterized, and synthesized, and two of them, the pentapeptide and the nonapeptide, have been studied both in vitro and in vivo (47-50). Both peptides are also bradykinin-potentiating agents. The results with the pentapeptide in hypertensive rats have shown a reduction in arterial blood pressure in two-kidney but not in one-kidney chronic renal hypertensive animals (47, 48) and, thus, the data agree with those obtained with the specific competitive antagonists of angiotensin II. Krieger et al. (48) have suggested the use of these peptides as a screening test to determine whether the renin-angiotensin system is contributing to the hypertensive state. The nonapeptide is preferable to the pentapeptide as a blocking agent because of its longer duration of action in vivo (47).

In the rabbit, immunization with angiotensin II fails to prevent or to modify appreciably the course of one-kidney renal hypertension (39, 40). Published data are not available from use of angiotensin II antagonists or converting enzyme inhibitors in hypertensive rabbits, but recent unpublished observations from our laboratory have revealed no change in arterial blood pressure with infusions (6 µg/kg min⁻¹) of 1-Sar-8-Ala-angiotensin II in unilaterally nephrectomized rabbits with renal (Goldblatt) hypertension of 1-2 months duration. The results of these two groups (52, 53) differed. In the studies of Pals and Masucci (52) in chronic perinephritic hypertensive dogs, the pentapeptide and the nonapeptide have been studied both in vitro and in vivo (47-50). Both peptides are also bradykinin-potentiating agents. The results with the pentapeptide in hypertensive rats have shown a reduction in arterial blood pressure in two-kidney but not in one-kidney chronic renal hypertensive animals (47, 48) and, thus, the data agree with those obtained with the specific competitive antagonists of angiotensin II. Krieger et al. (48) have suggested the use of these peptides as a screening test to determine whether the renin-angiotensin system is contributing to the hypertensive state. The nonapeptide is preferable to the pentapeptide as a blocking agent because of its longer duration of action in vivo (47).

In the dog, renal hypertension produced by renal artery constriction or by wrapping the kidney in cellophane (perinephritic hypertension) in unilaterally nephrectomized animals has been studied. The first observations were reported by Sweet et al. (51) with 1-Sar-8-Ile-angiotensin II; the pressor response to acute renal artery constriction is prevented but no reduction in pressure is observed in chronic perinephritic hypertensive dogs. By use of the nonapeptide converting enzyme inhibitor, Miller et al. (33) have also blocked the hypertensive response to acute renal artery stenosis, while plasma renin activity increased. In addition, both groups (33, 51) have observed a striking fall in arterial blood pressure in acute renal hypertensive dogs with the two different blocking agents. More recently, Pals and Masucci (52) and Johnson et al. (53) have reported a fall in arterial blood pressure during intravenous infusion of 1-Sar-8-Ala-angiotensin II in acute malignant hypertensive dogs with renal artery stenosis and elevated plasma renin activity. Collectively, these new data provide strong evidence that the renin-angiotensin system is involved in the initiation of acute renal hypertension in the unilaterally nephrectomized dog. These results are consistent with early observations (54, 55) that plasma renin activity is elevated during the acute phase of unilateral renal hypertension in the dog.

In chronic renal hypertension in dogs, evidence for a pathogenetic role of the renin-angiotensin system is lacking. The preliminary observations of Sweet et al. (51) in chronic perinephritic hypertension in dogs have been extended by Bumpus et al. (17). Again, 1-Sar-8-Ile-angiotensin II was given to conscious dogs with chronic perinephritic hypertension and to two dogs with renal artery constriction and hypertension of 10 and 15 days duration; arterial blood pressure failed to fall and, frequently, a prolonged agonistic pressor response occurred. In the studies of Pals and Masucci (52) and Johnson et al. (53), 1-Sar-8-Ala-angiotensin II was given to conscious dogs with renal artery constriction and chronic hypertension; the duration of the hypertension was not stated by Pals and Masucci (52) but Johnson and co-workers (53) studied animals with hypertension of 2-7 weeks duration. The results of these two groups (52, 53) differed. Pals and Masucci observed both small depressor effects and small sustained (<12 mm Hg) pressor responses; in contrast, Johnson et al. (53) observed a slight transient pressor response of 4-5 minutes duration followed by a return in arterial blood pressure to the control level where it remained for the 45 minutes of infusion of the analogue. This finding was consistent in all three chronic renal hypertensive dogs and in all five normal conscious dogs. This initial pressor response followed by a return to the control level of arterial blood pressure has also been observed in anesthetized normal dogs (4). The response probably reflects a direct myotrophic action on arteriolar smooth muscle. These results in chronic hypertensive dogs are in contrast to the initial findings (1-4) with 1-Sar-8-Ala-angiotensin II in low output states with hyperangiotensinemia in which the same dose of this analogue produces a striking drop in arterial blood pressure. These new observations with angiotensin II analogues are consistent with the findings from
the early reports (54, 55) of normal activity of the renin-angiotensin system in chronic renal hypertension in dogs.

The findings with these new blocking agents support the following ideas: (1) increased activity of the renin-angiotensin system occurs during acute renal artery constriction and is involved in the pathogenesis of both acute one-kidney (in rats and dogs) and acute two-kidney (in rats) hypertension, (2) increased activity of the renin-angiotensin system helps to maintain a high level of arterial blood pressure in chronic two-kidney hypertension in rats and (3) normal activity of the renin-angiotensin system is present in chronic one-kidney hypertension in rats, rabbits, and dogs. These negative data on the role of the renin-angiotensin system in chronic one-kidney hypertension indicate the need for further study of the pathogenesis of this experimental disease.

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