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BRIEF REVIEWS

The Pathogenesis of Chronic Renovascular Hypertension

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THE ROLE of the kidney in the regulation of arterial pressure was recognized as early as 1898 when Tigerstedt and Bergman demonstrated that kidney extracts possess a pressor action and gave the name renin to the substance producing the action. In 1934, Goldblatt and co-workers[1] produced chronic renal hypertension in dogs by renal artery constriction. This discovery was a major breakthrough because it provided an easy and reliable method to produce a model of human renovascular hypertension. Almost immediately, investigators began to search for a humoral mechanism to explain the pathogenesis of experimental renal hypertension. This search culminated in the discovery of the renin-angiotensin system in 1939 almost simultaneously by Page and Helmer[2] in the United States and by Braun-Menendez and collaborators[3] in Argentina.

For four decades the complicated problem of renal hypertension has been investigated in attempts to define the pathogenic mechanisms, and much emphasis has been placed on the renin-angiotensin system. It seems clear that the response to renal artery stenosis differs among species. In man, there is considerable evidence for a primary role for the renin-angiotensin system in chronic renal hypertension, whereas in the dog, rabbit, and rat the pathogenic mechanisms appear to differ. Also, there is an increasing body of evidence which suggests that humoral mechanisms other than the renin-angiotensin system are important in the pathogenesis of hypertension secondary to renal artery constriction in the dog, rabbit, and rat. These animal models of renal hypertension serve a very useful role in the investigation of the mechanisms operative in the patient with renovascular hypertension. It is the purpose of this review to present an analysis of the data bearing on the possible primary pathogenic mechanisms in renovascular hypertension.

The Role of the Renin-Angiotensin System

It is well known that patients with renal artery stenosis and hypertension have increased activity of the renin-angiotensin system. Indeed, the presence of an increase in renin activity in renal vein blood from the involved kidney has become one of the very best diagnostic indicators of the disease.[4] Furthermore, the recent evidence[5] from observations during angiotensin II blockade indicates that there is increased activity of the renin-angiotensin system in patients with renovascular hypertension. Streeten and associates[5] made observations with [Sar^1,Ala^8]angiotensin II under carefully controlled conditions and this is imperative for the results to be meaningful. This angiotensin II-blocking agent has an agonistic action under some conditions in man,[5, 6] and this must be considered in the plan of the experiment and in the interpretation of the results. The question of the involvement of the renin-angiotensin system in human renal hypertension is complicated by reports[4] of the apparent occasional occurrence of normal plasma renin activity (PRA) from assay of peripheral blood of patients with renovascular hypertension; the certainty of the diagnosis was proved by repair of the renal lesion or nephrectomy and cure of the hypertension. It should be emphasized that it is easy to obtain a false-negative normal value for PRA because of the many factors which decrease PRA, errors in methodology, and a decreased rate of renin secretion by the contralateral kidney. Normal renal vein renin ratios between the two kidneys have also been obtained when the stenosis involved a segmental branch and blood from the main renal vein diluted the blood from the ischemic area. It should also be pointed out that it is entirely possible that some of the reports that PRA is normal in human renovascular hypertension are correct and that another renal pressor mechanism exists. Indeed, Skeggs et al.[7, 8] have new evidence for another such renal pressor mechanism in rabbits with one-kidney renal hypertension. Unfortunately, however, one cannot extrapolate from an experimental model to the patient, a point which emphasizes another difficulty in trying to unravel this complicated problem. Since the response to renal artery stenosis varies substantially among species, the animal models do provide excellent and unique experimental situations in which to look for another renal pressor mechanism which might be present in the patient with renovascular hypertension.

In the rat, the response to renal artery stenosis is apparently similar to that in man; constriction of one renal artery with the other kidney intact produces chronic hypertension with an elevated PRA, and the animals are responsive to angiotensin II blockade.[9, 10] There is, however, one report[11] that after 15 weeks of two-kidney hy-

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pertension in the rat angiotensin blockade failed to reduce arterial pressure unless the rats were sodium-depleted. Unilaterally nephrectomized rats with the remaining renal artery constricted have a volume-dependent type of hypertension with normal activity of the renin-angiotensin system.[9, 10] In the rabbit, the situation is quite different; PRA is usually normal [12, 13] and rabbits with both one- and two-kidney chronic hypertension are frequently unresponsive to angiotensin II blockade.[12, 13] Occasionally, however, PRA is elevated and rabbits with both one- and two-kidney hypertension have responded to competitive antagonists such as [Sar^1,Ala^8]angiotensin II.[12-14] It is interesting that rabbits with chronic two-kidney hypertension frequently have a spontaneous natriuresis in association with the rise in PRA and responsiveness to angiotensin II blockade.[13] The natriuresis is associated with an unusually high arterial pressure; therefore it appears to be a pressure natriuresis.

In the dog, the response to renal artery stenosis differs still further from that in rat, rabbit, and man. For many years, the only model of renal hypertension used in the dog was the one-kidney model. In chronic one-kidney hypertension, PRA was normal[15] and angiotensin II antagonists failed to lower arterial pressure.[15] In 1972 Lupu and Maxwell[16] demonstrated that a reduction of renal blood flow to 20% in one kidney produced chronic hypertension in the dog in the presence of the contralateral intact kidney. The usefulness of this procedure has recently been evaluated by Watkins et al.[17] They observed chronic hypertension of 30 days' duration in 50% of a series of 10 dogs subjected to this procedure; three of the five dogs with hypertension continued to have an elevation in arterial pressure for another 15-30 days. At this time, these three dogs showed a decline in arterial pressure toward or to the control level. An exploratory laparotomy was performed on all three dogs and capsular collateral vessels were observed in each; these vessels were ligated and the hypertension reappeared. So, apparently, the occurrence of collateralization limits the duration of hypertension in the dog. Masaki et al.,[18] in a recent preliminary report, have also recognized the important role of collateralization in preventing the development of sustained hypertension in the dog. In dogs with chronic two-kidney hypertension, PRA was normal[17, 18] and the dogs failed to show a decrease in arterial pressure in response to angiotensin II blockade. However, sodium depletion converted these dogs from angiotensin-independent to angiotensin-dependent hypertension as shown by an excellent depressor response to [Sar^1,Ala^8]angiotensin II.[17]

To summarize this section, there is evidence for a primary pathogenic role of the renin-angiotensin system in renovascular hypertension in man and in the two-kidney model in the rat. Other as yet undefined mechanisms appear to play a primary role in one-kidney hypertension in the rat and in one- and two-kidney hypertension in the rabbit and the dog. There is increasing evidence for a renal pressor mechanism other than the renin-angiotensin system in experimental renal hypertension; investigators should continue to look for such a system in the patient with renovascular hypertension.

Other Possible Pressor Mechanisms

About 10 years ago McPhaul and associates[19] reported evidence that a renal pressor agent other than renin is responsible for surgically remediable renovascular hypertension. These observations on man were extended to experimental models of renal hypertension in the dog and rat. Grollman and Krishnamurty[20] suggested the name nephrotensin for the newly described pressor agent in renal venous blood; this material was concentrated in an ammonium sulfate fraction of plasma. It was reported[21] that the material was not inactivated by angiotensin I antibodies and that it could be differentiated from angiotensin I and II by the blood pressure response in the rat and by its influence on perfusion pressure in the isolated rabbit's ear.

This factor of Grollman was studied thoroughly by Schweikert et al.,[22] who found it to be angiotensin I bound to an α_2-globulin. Whenever pressor activity was found on bioassay, a comparable amount of preformed immunoreactive angiotensin I was present in renal venous blood from the kidney with the stenotic renal artery. The incubation in vitro of the renal pressor substance with angiotensin I antisera resulted in complete inactivation. Treatment of the substance with converting enzyme resulted in loss of immunoreactivity while pressor activity was retained. Finally, electrophoretic studies suggested that the substance was angiotensin I bound to an α_2-globulin.

These observations of Schweikert et al.[22] were convincing and it seemed that the nature of the Grollman factor had been defined. However, in 1975, Susic and Sparks[23] appeared to reopen the question by studies with angiotensin II blockade. They found that the pressor activity of nephrotensin was not altered by previous immunization of test animals with angiotensin II or by pretreatment with an angiotensin I-converting enzyme inhibitor.

It has been known since 1953 that active immunization of chronic renal hypertensive animals with kidney extracts produced a reduction in arterial pressure. This evidence for the renin mechanism has not been convincing because of the possibility that a substance other than renin produced the effective antibody, or a nonspecific response could have occurred. Skeggs et al.[7, 8] have reinvestigated the possibility of a nonrenin pressor substance in kidney extracts. They found a consistent reduction in arterial pressure in one-kidney renal hypertensive rabbits immunized with hog kidney extracts. In contrast to previous reports, Skeggs et al.[7] found a very poor correlation between the level of plasma antirenin titer and the fall in arterial pressure. Also, both angiotensin II blockade and passive immunization failed to lower arterial pressure in the rabbits with chronic hypertension but antisera did block the arterial pressure response to exogenous renin. Skeggs et al.[7] suggested the possibility of a pressor mechanism other than the renin-angiotensin system to explain the hypertension. In their most recent publication, this group[8] reported a lowering of arterial pressure in response to active immunization with a protein from a nonrenin fraction of kidney extracts in rabbits with chronic one-kidney renal hypertension. The evidence from this study

has been interpreted to suggest that an unknown substance produced an antibody that neutralized this unknown factor which is essential for maintenance of chronic one-kidney hypertension in the rabbit. This appears to be a fruitful approach and additional new evidence is awaited with interest.

Antihypertensive Factors

Many lines of evidence suggest that antihypertensive mechanisms are involved in the pathogenesis of renovascular hypertension. In the dog, constriction of one renal artery with the other kidney intact frequently leads to a transient elevation in pressure; removal of the intact kidney results in sustained hypertension. This observation indicates an antihypertensive function for the intact kidney. Also, there is the well established phenomenon of a pressure natriuresis which seems to be related to the intact kidney in rabbits, sheep, and rats. There is much evidence to indicate that part of the antihypertensive function of the kidney is attributable to its influence on extracellular fluid volume, and very recently Pamnani et al.[24] have provided evidence that prostaglandins are released from the intact kidney in dogs with two-kidney hypertension. Several different substances, including prostaglandins A and E (GPA and PGE), the antihypertensive neutral renomedullary lipid of Muirhead, and the renal kinins have been considered as possible factors to mediate the antihypertensive mechanism.

Both PGA and PGE dilate blood vessels and lower blood pressure. In considering this action in the pathogenesis of hypertension, prostaglandins might exert an effect either by a decrease in their level in circulating blood or by a decrease in their local concentration in blood vessel walls. In addition, prostaglandins increase renin secretion and they appear to modulate renal blood flow,[25] renal tubular sodium reabsorption,[25] and the concentration of sodium in the renal medulla.[26]

There is general agreement that PGE_2 in snythesized in the kidney but controversy exists about the formation of PGA.[25] This is an important question because there is little destruction of PGA in passage through the lungs. Consequently, a high plasma level of PGA could exert an important influence on blood pressure. Lee and Attallah[27] suggested that the kidney is the primary source of PGA_2 and pharmacological studies have demonstrated a natriuretic action of this prostaglandin. Lee and Attallah[27] and Zusman et al.[28] reported a decrease in the plasma level of PGA in patients with essential hypertension.

On the other hand, several workers (cited by Anderson et al.[25]) have been unable to determine PGA in renal tissue or in systemic or renal venous blood in man; even with the most sensitive method (mass spectroscopy) some investigators[29] have failed to detect PGA in blood. It has been suggested that PGA might be an artifact formed in renal tissue by conversion of PGE to PGA, and in a recent review Lee et al.[30] concluded that PGA_2 has not been demonstrated to be present in human plasma. Also, the importance of a high plasma level of PGE_2 has been questioned, since this compound is very effectively inactivated by the lungs. More information is needed to define the plasma level of PGE_2 in patients with hypertensive disease.

The other possible action of prostaglandins, that exerted at the local level in the arteriolar wall, has received increasing attention. It has been proposed that prostaglandins might interfere with the local release of norepinephrine,[31] or blunt the vascular response to the angiotensins[32] and norepinephrine.[33] It is also well known that the angiotensins stimulate PGE synthesis. It appears, therefore, that under normal homeostatic conditions a balance exists between the actions of the prostaglandins and vasoconstrictor substances on arteriolar smooth muscle. In hypertension, this balance could be disturbed with the net result that arteriolar constriction occurs.

One of the most intriguing developments in the field of antihypertensive factors is the finding by Muirhead et al.[34] that auto- or isotransplants of renal medullary tissue lowered arterial pressure in animals with renal hypertension. They implanted this tissue either subcutaneously or intraperitoneally in dogs, rats, and rabbits and observed a fall in arterial pressure to control levels; this response was maintained until the transplanted tissue was removed. Dead renomedullary tissue had no effect. This evidence indicates that cells of the renal medulla exert a nonexcretory, antihypertensive action. Muirhead has suggested that the mechanism is mediated by an antihypertensive neutral lipid produced by the renal medullary interstitial cells. It should be pointed out, however, that there also is evidence that prostaglandins are produced by these interstitial cells. Finally, there remains unanswered the question of the actual role of a renal medullary antihypertensive factor in the pathogenesis of hypertension.

Several studies have examined the relationship of the kallikrein-kinin system to the pathogenesis of renal hypertension. Observations on rats,[35] dogs,[35] and patients with renovascular hypertension[35] showed a striking decrease in the urinary excretion of kallikrein, and the kallikrein content of kidney tissue was decreased in rats with renal hypertension.[36] In patients, the decrease appeared to be related to the stenotic side,[35] and detailed studies[35] on dogs with unilateral renal artery stenosis revealed a close correlation between the degree of reduction in urinary kallikrein and the decrease in renal blood flow. These data suggest the possibility that kinins such as bradykinin might modify the initiation and maintenance of renal hypertension but additional studies are needed to define a role for the kallikrein-kinin system.

Cardiac Output, Body Fluid Volume, and the Theory of Whole Body Autoregulation

In 1964 Ledingham and Cohen[37] reported that a transient elevation in cardiac output occurred for a few days after renal artery constriction in unilaterally nephrectomized rats developing hypertension. They proposed that the hypertension was a new equilibrium state achieved in response to the transient elevation in cardiac output and maintained by an increased myogenic response in the arterioles. Guyton and associates[38, 39] have championed this concept; although most of their work has been in volume-loading hypertension, this group[38, 39] has also sug-

gested that the same sequential changes occur in renovascular hypertension. In the schema proposed,[38, 39] retention of salt and water by the kidney leads to increased blood volume, increased mean circulatory pressure, and an elevation in mean right atrial pressure which impacts on the myocardium to increase cardiac output. It has been suggested[38] that peripheral arteriolar constriction occurs in response to the increase in blood flow to peripheral tissue, a process termed whole body autoregulation. Although it has also been reported[40] that cardiac output is increased in the dog with the development of renal hypertension, in the rabbit measurements of cardiac output have failed to show an increase.[41]

This is an attractive theory but a number of findings appear to be irreconcilable with it. As an example, it has been found[42] that chronic sustained hypertension secondary to renal artery constriction occurred in unilaterally nephrectomized sodium-depleted dogs on a low (less than 3 mEq/day) sodium diet in the absence of sodium and water retention. These observations were confirmed[43] and, more recently, chronic hypertension was observed in sodium-depleted dogs on a low sodium intake in response to wrapping the kidney with cellophane to produce perinephritis.[44] Also, in studies by Tarazi and associates,[45] stellate ganglion stimulation for 7 days in conscious dogs produced a rise in arterial pressure and the response was initiated by a transient increase in cardiac output. This finding suggested the possibility of whole body autoregulation but when the increase in cardiac output was prevented by β-blockade during stellate stimulation, the same rise in arterial pressure occurred and was attributable solely to increased total peripheral resistance. It should be emphasized that the occurrence of whole body autoregulation over any extended period of time has not been demonstrated experimentally.

The introduction of maintenance dialysis after bilateral nephrectomy for the management of chronic uremia has provided an opportunity for evaluation of the theory of whole body autoregulation in man. Onesti and co-workers[46] observed a sharp difference in the blood pressure response to salt and water loading between previously normotensive and previously hypertensive anephric patients. The former group failed to elevate their blood pressure whereas the previously hypertensive group showed a progressive increase in blood pressure that reached hypertensive levels. The authors concluded that the vasopressor function of the kidney is the most important factor in the pathophysiology of hypertension in end-stage renal disease.

These observations on patients loaded with salt and water emphasize the interlocking relationship between volume and peripheral resistance in the control of arterial pressure, and Laragh[47] has championed this idea in his volume-vasoconstriction hypothesis. It is quite clear that the pressor effects of the renin-angiotensin system are influenced by the state of sodium balance. The importance of volume per se is exemplified in the experiments of Coleman and Guyton,[48] who have produced hypertension by salt and water loading in dogs with a reduced renal mass. Also, removal of the renal artery clip in one-kidney hypertension in the dog was followed by striking natriuresis and decrease in blood volume as the blood pressure fell.[49] All of these observations show that the level of body fluid volume is a determinant of the level of arterial pressure. On the other hand, in both sheep[50] and rats,[51] removal of the renal artery clip in animals with one-kidney hypertension was followed by a decrease in arterial pressure and this change was not related to loss of salt and water in urine. Finally, it should also be emphasized that increased plasma angiotensin II increases the plasma level of aldosterone in the patient with chronic renovascular hypertension and that the increase in body fluid volume is mediated via the renin-angiotensin-aldosterone system.

Neurogenic Factors

Many types of evidence suggest some role for the sympathetic nervous system in renal hypertension and, in recent years, reports[52–54] have indicated that the central nervous system could be involved. It is easy to visualize that a centrally mediated increase in sympathetic nervous activity occurs in the patient with hypertension who is hyperresponsive to various stimuli. The potent action of and effective responses to drugs which inhibit the sympathetic nervous system are consistent with a pathogenic role for this system in hypertension.

In renal hypertension, investigators have tried to implicate a role for angiotensin II at the level of the sympathetic nerve terminals and in special areas of the brainstem such as the area postrema. It has been suggested that angiotensin II facilitates the release of norepinephrine at the sympathetic nerve ending; another possible mechanism is that angiotensin II decreases the reuptake of norepinephrine released into the synaptic cleft. If either mechanism is operative, the net result would be to increase the amount of norepinephrine available to react with vascular smooth muscle. Thus, a peripheral neurogenic action of angiotensin might be to intensify the cardiovascular responsiveness to efferent sympathetic discharge. In the patient with renovascular hypertension and hyperangiotensinemia, this mechanism must be considered; there is, however, no firm evidence to demonstrate its existence.

The possible importance of a central nervous system area sensitive to angiotensin was most convincingly suggested by the long-term infusion of angiotensin II into conscious rabbits; Dickinson and Yu[53] found that the intravertebral arterial infusion of angiotensin in a low dose increased arterial pressure, whereas the same dose given systemically was ineffective. The area sensitive to angiotensin was localized to the area postrema because the response to intravertebral infusion of the peptide was prevented by bilateral ablation of the area postrema.[54] Also, Ferrario and McCubbin[52] have presented evidence for another angiotensin-sensitive area at a higher level in the brainstem. Finally, there is the recent preliminary report by Brody et al.[55] that ablation of a small discrete area of the brainstem just anterior to the 3rd ventricle prevents the development of renal hypertension in the rat.

Although there are many types of suggestive evidence for a role for the sympathetic nervous system, this system is not essential for renal hypertension to occur. Many years ago, it was demonstrated that immunosympathectomized rats developed hypertension when given mineral-

ocorticoids and a high salt diet. Douglas et al.[56] have demonstrated that chronic renal hypertension developed in rats in which the peripheral sympathetic nervous system was completely ablated by chronic guanethidine administration and adrenal demedullation. It might be argued that with deletion of the sympathetic nervous system other compensatory mechanisms become involved, but this does not seem to be a reasonable explanation for the maintenance of a hypertensive process. These considerations indicate that sympathetic nervous function may represent one of the many factors involved in renovascular hypertension but there is nothing yet to demonstrate that this is a primary mechanism.

Changes in Vascular Smooth Muscle

In addition to the extrinsic factors already discussed, there is substantial evidence that intrinsic changes in vascular smooth muscle increase peripheral resistance. These alterations have been attributed to altered vascular reactivity of the smooth muscle in the arteries and arterioles and to changes in the geometry of the vessel wall. Bohr[57] pointed out that altered vascular reactivity could involve two aspects of the contractile process: (1) excitability might be increased so that a given response is elicited by a lesser vasoconstrictive stimulus, and (2) contractility, which defines the force generated for a given set of mechanical conditions, might be increased. In his model for incorporating vascular smooth muscle in the control of arterial pressure, Jones[58] has emphasized that bioregulants such as norepinephrine produce increased responses of vascular smooth muscle from hypertensive animal models. Folkow[59] has championed the geometric hypothesis which considers that the decreased internal radius of the peripheral arteriole increases the mechanical advantage of vascular smooth muscle so that an augmented response occurs.

Unfortunately, most of the experiments designed to examine these hypotheses have been made on deoxycorticosterone acetate (DOCA) or spontaneously hypertensive rats rather than on animals with renal hypertension. Bohr[57] has reported an increase in spontaneous rhythmicity in femoral artery strips of animals with renal hypertension compared to normal controls and he observed increased reactivity in response to both potassium chloride and epinephrine. Many years ago, Tobian[60] dissected out arterioles and found an increase in the sodium, potassium, and water content of these vessels from rats with renal hypertension compared to normotensive controls. Studies of cell sodium in arteries[61] and potassium fluxes (A.W. Jones, personal communication) in vascular smooth muscle from rats with renal hypertension have failed to show an alteration. However, in small mesenteric arteries and veins from dogs with one-kidney perinephritic hypertension, ^{86}Rb uptake was decreased in comparison to the results from normotensive dog vessels.[62] These observations indicate that the activity of a ouabain-sensitive Na^+-K^+ pump is depressed in vascular tissue from chronically hypertensive dogs. These findings were interpreted to suggest partial depolarization of the smooth muscle cell membrane which would favor an increase in vascular resistance.[62]

It is clear that additional studies are needed before we can understand the cellular and subcellular changes in vascular smooth muscle in relation to hypertension. The nature of vascular smooth muscle reactivity must be more exactly defined. The consensus seems to be that the structural changes in the arteriolar wall are a consequence rather than a cause of hypertension. Investigations are needed to permit the synthesis of both the functional and structural approaches to altered vascular reactivity so that we can have a better overview of how altered vascular reactivity increases total peripheral resistance and results in hypertension.

In summary, this analysis of the many factors which influence arterial pressure serves to emphasize that renovascular hypertension is multifactorial in nature as Page[63] has emphasized for many years. However, in most patients with renovascular hypertension the renin-angiotensin system appears to be a primary pathogenic mechanism; repair of the renal lesion or removal of the involved kidney frequently leads to a decrease in PRA to normal and to a cure of the hypertension. In contrast, in several of the hypertensive animal models evidence is lacking to show that the renin-angiotensin system is involved in the maintenance of chronic renal hypertension; instead, there is new evidence that another renal pressor mechanism is involved. Antihypertensive factors such as prostaglandins and the renomedullary neutral lipid appear to be involved but it is unclear as to their specific role in the causation of renal hypertension. Evidence is lacking to support the hypothesis of whole body autoregulation in renovascular hypertension. When there is increased activity of the renin-angiotensin system in renovascular hypertension, as in man, both the sympathetic and central nervous systems conceivably could be involved. There is evidence for altered vascular reactivity in arterial tissue of animals with renal hypertension but neither the basic cellular mechanisms involved nor the role of the changes in the pathogenesis of hypertension are known.

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