REVIEW

The renin–angiotensin system and the pathogenesis of vascular disease in malignant hypertension

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Summary

1. The syndrome of malignant hypertension in man and animals has three fundamental components: high blood pressure, activation of the renin–angiotensin system and the rapid development of necrotizing arteriolar disease.

2. The high blood pressure can be associated with different conformations of the arteriolar microcirculation. The emergence of an arteriolar reaction pattern characterized by the formation of focal dilatations, with intervening constricted segments, is of fundamental pathophysiological importance.

3. Activation of the renin system is reflected in an increased renin secretion rate from the kidneys and an increased rate of angiotensin II generation in the pulmonary vascular bed.

4. The crucial pathogenetic process, leading eventually to severe arteriolar wall damage, is a penetration of plasmatic macromolecules into the wall of distended arteriolar segments, as observed in states of severe experimental hypertension.

5. Renin can induce vascular disease, but hypersecretion of renin is not a necessary condition for the development of hypertensive arteriolar necrosis.

Key words: angiotensin II, angiotensin II generation rate, arteriolar lesions, malignant hypertension, plasmatic vasculosis, renin, 'sausage-string' pattern, vascular permeability.

The syndrome of malignant hypertension is characterized by a very high blood pressure, activation of the renin–angiotensin system and rapid progression of necrotizing arteriolar disease. The complicated relations among these three salient features can be analysed to a certain extent on the basis of the available evidence, but several pieces of the puzzle are still lacking.

High blood pressure and vascular reaction patterns

The high blood pressure is due to an abnormal state of constriction of the resistance vessels. However, this is not a sufficient description of the condition of the arteriolar microcirculation. Studies by vital microscopy in animals with severe acute or chronic hypertension have shown that simple uniform narrowing of small arteries and arterioles is not the only mode of reaction. In addition, a peculiar pattern of alternating constrictions and dilatations can be observed.

In the author's view, this particular arteriolar reaction pattern is a phenomenon of considerable importance for the understanding of the vascular pathophysiology of malignant hypertension (Byrom, 1969; Giese, 1966). It is appropriate to recall Byrom's classical papers containing precise descriptions and perfect documentation of these microcirculatory events (e.g. Byrom, 1954). Over the years, several investigators have confirmed and extended these early observations. The collected evidence strongly supports the contention that the emergence of this pattern of focal bead-like dilatations, with intervening constricted segments, along the course of the small arteries and arterioles is of common occurrence in severe experimental hypertension (Giese, 1973).

Activation of the renin–angiotensin system: dynamic aspects

The second cardinal feature of malignant hyper-
tension is activation of the renin system. Evaluation of the state of the renin system is usually based upon determination of renin activity or renin concentration in a plasma sample. In a conceptual context, it is of some interest to relate the information derived from such essentially static measurements to the data obtained by more direct approaches to the assessment of the dynamic state of the renin-angiotensin system.

In patients with unilateral renal or renovascular disease, the renin secretion rate from the diseased kidney can be assessed by determination of the veno-arterial renin gradient across the kidney and measurement or estimation of the renal plasma flow. It has been shown that there is a significant correlation between plasma renin concentration, as measured in a sample from a peripheral artery, and the estimated renin secretion rate (Giese, Aurell & Munck, 1972).

Another kinetic variable is the generation rate for angiotensin II within the human pulmonary vascular circuit. The transpulmonary angiotensin II generation rate can be assessed by determination of the arterio-venous gradient for angiotensin II across the lungs with simultaneous measurement of the pulmonary plasma flow.

In a group of patients with renovascular or unilateral renal disease, the correlation between the systemic plasma renin concentration and the rate of angiotensin II generation within the pulmonary vascular bed proved to be highly significant (Fig. 1). Thus the dynamic events of angiotensin II generation were truly reflected in the static plasma renin concentration measurement (J. Giese, A. M. Kappelgaard, K. H. Tønnesen & J. O. Lund, unpublished observations).

Arteriolar disease

Next, the third component of the syndrome can be examined: the advent of arteriolar necrosis in acute malignant hypertension. There is now a considerable body of experimental evidence to show that there is a close relation between the emergence of the arteriolar reaction pattern previously described (colloquially known as the 'sausage-string pattern') and the development of malignant fibrinoid arteriolar lesions (Giese, 1973). It has been shown by many investigators that this microcirculatory reaction pattern is associated with the development of focal abnormalities of arteriolar wall permeability (Giese, 1964; Goldby & Beilin, 1974). Briefly stated, the distended arteriolar segments become the seat of plasmatic insudation, that is a penetration of plasmatic macromolecules into the arteriolar wall takes place in the dilated segments along the course of the arterioles, whereas the constricted parts are not affected.

These focal abnormalities of mural permeability can be demonstrated by macromolecular tracers such as fluorochrome-labelled plasma proteins (Giese, 1961). Whereas the dye-labelled plasma proteins do not penetrate into the arteriolar walls of normal rats, quite impressive deposits can be demonstrated in rats exposed to acute hypertension, as induced by infusion of angiotensin II or by the application of tight silver clips to both renal arteries.

Another technique, which is particularly well suited for microscopical studies in vivo, is based upon the use of colloidal carbon particles for demonstration of abnormal permeability of the arteriolar wall (Majno, Palade & Schoefl, 1961; Giese, 1964; Goldby & Beilin, 1972; Thorball & Olsen, 1974).

In conclusion, there are very good reasons for assuming an intimate relationship between the emergence of focal arteriolar dilatations, the influx of plasmatic macromolecules into the arteriolar wall and the subsequent development of focal arteriolar wall damage.
Renin and vascular disease

A number of the experimental observations referred to have been obtained in animals with acute hypertension induced either by activation of the endogenous renin system or by exogenous administration of renin or angiotensin II. Obviously, renin can induce vascular disease. However, observations in animals with so-called renoprival hypertension have shown that neither hypersecretion of renin nor even the presence of the kidneys are necessary conditions for the experimental induction of hypertensive arteriolar necrosis. In certain experimental models of hypertensive disease the renin system is suppressed, but nevertheless severe arteriolar lesions are consistently produced. Furthermore, other pressor agents can induce vascular reaction patterns and arteriolar lesions much like those induced by renin or angiotensin II (review: Giese, 1973).

Future research

As a final note, some relevant objects for future research can be defined. In particular, the microcirculatory mechanisms conducive to the emergence of the arteriolar constriction–dilatation pattern should be thoroughly investigated, due attention being paid to the relative importance of intrinsic vascular mechanisms, vasoactive substances and mechanical factors respectively. Also, further studies on the effects of plasmatic insudation on the arteriolar wall structures are needed.

An all-important question is whether the experience obtained from animal experiments can be readily applied to the understanding and interpretation of microcirculatory events in human hypertensive disease. This question implies the need for much more information on the presence or absence of similar vascular reaction patterns in hypertensive man.

References


