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Editorial Comment

Development of Genetic Hypertension Is There a “Critical Phase”?

Thomas Unger and Rainer Rettig

A juvenile 16-year-old individual, known to be genetically hypertension-prone, receives a 6-month treatment with a specific antihypertensive agent – or a cocktail of several agents – and as a result is cured from hypertension and its sequelae for the rest of his life. This, of course, is a futuristic scenario. But it could come close to reality if we were to identify a “critical phase” during the development of hypertension that is sensitive to pharmacological interference with blood pressure regulation in a way that alters the long-term course of the disease.

In this issue of *Hypertension*, Harrap and coworkers¹ report that a 4-week period of antihypertensive treatment with the angiotensin converting enzyme (ACE) inhibitor perindopril during the developmental phase prevented the full expression of hypertension in adult spontaneously hypertensive rats (SHR). This effect was due to a reduction of total peripheral resistance consistent with a reduced media-to-lumen ratio of mesenteric resistance vessels. Plasma renin and angiotensin II (Ang II) were not different between adult pretreated SHR and control SHR. The presence of exogenous Ang II during the treatment period prevented the long-term blood pressure-reducing effects of the ACE inhibitor. When the drug was given for a shorter period of only 1 week during development of hypertension or for a period of 4 weeks after hypertension was established, no significant long-term effects on blood pressure were observed. As is generally the case with stimulating papers, there are more questions than answers emerging from this study, including the following: 1) Is there a critical phase in the development of genetically determined hypertension during which interference with blood pressure has beneficial long-term effects? 2) Does this “window” last throughout the development of high blood pressure, or can it more closely be associated with certain phases of the development of hypertension? 3) What accounts for the beneficial long-term effects: Is it the reduction in blood pressure per se during the critical phase, or is it the interference with a particular hypertensinogenic factor or mechanism? 4) More specifically: Is Ang II such a factor, and if yes, how does this peptide exert its action? 5) Are there other

genetic hypertension-inducing factors that can specifically be antagonized? 6) Is the critical phase associated with the development of genetic hypertension in SHR only, or does it represent a general feature of hypertension development? 7) Last but not least, how much do these experimental results contribute to our understanding of human hypertension?

Coming back to the first question, the results of the study by Harrap et al¹ demonstrate convincingly that lowering blood pressure in 6–10-week-old SHR by an ACE inhibitor prevents the full expression of hypertension, though not the increase in blood pressure as such. This effect was obviously due to a permanent reduction in total peripheral resistance. The finding of a reduced media-to-lumen ratio in the mesenteric vessels suggests that structural changes (i.e., regression of vascular hypertrophy) had caused the beneficial effect in vascular function. Although it appears that these data favor the “structural” hypothesis – that structural vascular changes (induced by hypertension) give rise to further increases in blood pressure and, vice versa, that a reduction of vascular media thickness engenders a permanent blood pressure reduction – there are still many questions to be answered: For instance, why was there no alteration in the sensitivity of mesenteric resistance vessels in the treated animals despite the structural changes? Why was there so little effect on coronary and diaphragmatic vascular resistance? Why was the overall permanent reduction of blood pressure not greater than just 25–30 mm Hg?

With respect to the second question, the “time window,” the study seems to give more clear-cut answers: The intervention was successful during hypertension development and when treatment lasted for a period of more than 1 week. On first glance, this sounds reasonable – the intervention has to take place before significant structural vascular changes have occurred. But on second glance, questions come up again: If media hypertrophy is generally reversible, why is the intervention not successful after the establishment of high blood pressure? What brings this continuous process of intricate structural and functional vascular alterations to the point of no return, so that lowering blood pressure after this point does not produce long-term antihypertensive effects any more? What happens if the intervention takes place even earlier than the second week of life, for instance during fetal life?

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Things become even more difficult when one approaches the third question aiming at the specificity of the effect observed. An ACE inhibitor was used in the study to lower blood pressure, but no other antihypertensive agents were tested. Evidence from the literature suggests that in SHR other drugs like hydralazine, calcium entry blockers, or β -blockers are less likely than ACE inhibitors to induce permanent blood pressure reductions, but there are only a few studies in which this question was specifically addressed.² Comparative studies are needed aiming at the question as to whether the effect of the ACE inhibitor was specifically due to the elimination of Ang II (or the potentiation of kinins?) during a critical phase of blood pressure development or, unspecifically, due to the antihypertensive effect during this phase.

Harrap et al¹ recognized the importance of this point and included an experiment in the study in which the administration of a moderate pressor dose of Ang II during antihypertensive treatment prevented the long-term effects of the ACE inhibitor on blood pressure and vascular structure. This additional finding could be interpreted to mean that the effects of the ACE inhibitor were specific to Ang II in that the drug inhibited the generation of Ang II as a growth factor. Although this is a very attractive view, it may, as the authors indicate, be prematurely conceived: First, the study lacks an appropriate control with another endogenous pressor agent such as norepinephrine; second, most endogenous pressor substances appear to have some growth factor-like features; and third, the physiological or pathophysiological relevance of Ang II as a growth factor remains to be established. Nevertheless, be it as a growth factor or via different mechanisms, Ang II remains a candidate in the exclusive circle of gene products that account for genetic hypertension. This fact has recently gained support by the demonstration of hypertension in transgenic rats carrying the mouse *Ren-2* renin gene.³ Interestingly, as in the study by Harrap et al,¹ no obvious alterations in plasma Ang II or plasma renin were observed in the transgenic animals. These observations provide further support to the contention that paracrine rather than endocrine Ang II may be involved in long-term blood pressure control.^{4,5}

The renin-angiotensin system constitutes only one of several factors involved in genetic hypertension. So far, most of these factors have not been systematically tested for the presence of a critical phase during which they could successfully be antagonized as has been suggested for the renin-angiotensin system in the study by Harrap et al.¹ But there is indirect evidence that a critical phase may also exist for these factors. In renal transplantation studies, renal grafts from SHR donors have been shown to carry some yet unidentified information to induce hypertension in normotensive recipients.⁶ Whatever the nature of this factor, it is already expressed in SHR kidneys as young as 6 weeks of age. Recently, renal cytochrome P-450-dependent metabolites of arachidonic acid

have been demonstrated to be elevated in the kidneys of young but not adult SHR.⁷

Selective renal depletion of cytochrome P-450 by stannous chloride decreased blood pressure in young but not adult SHR. These data suggest that there may be a critical phase during which renal cytochrome P-450 may be important for blood pressure development in SHR. The long-term effects of an interference with this factor during the critical phase are currently unknown. Similarly, increased sympathetic nerve activity and exaggerated smooth muscle reactivity are frequently cited genetic factors in SHR that seem to be particularly active during the development of high blood pressure and less important once hypertension is established. For instance, it has recently been reported that norepinephrine concentrations and turnover in several cardiovascular tissues are particularly high in young SHR during the development of hypertension.⁸ The high catecholamine concentrations could potentiate the trophic effects of growth factors in early vascular hypertrophy and thereby contribute to blood pressure elevations during a critical phase. Further studies are warranted to investigate whether interference with adrenergic signal transduction during a yet unidentified critical phase may have long-term beneficial effects on blood pressure in hypertension-prone subjects.

Finally, the question remains whether the existence of a critical phase is a general feature of the development of hypertension or whether it is restricted to genetic hypertension in SHR. This problem needs to be addressed as well as the obvious question of the applicability of these experimental data to human hypertension.

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KEY WORDS • genetic hypertension • antihypertensive agents • blood pressure