Recent linkage studies in humans with essential hypertension and in animal models of spontaneous hypertension have suggested that genetically determined variation in the activity of the renin-angiotensin system may contribute to inherited variations in blood pressure (1, 2). While it is remarkable that most of the positive linkage studies of hypertension to date have implicated chromosome regions that contain genes of the renin-angiotensin system, such studies cannot prove that genetically determined alterations in the renin-angiotensin system contribute to the pathogenesis of spontaneous forms of hypertension. However, selective breeding experiments and gene transfer techniques may be used to investigate directly whether variation in specific DNA sequences can affect blood pressure.

In the current issue of *The Journal of Clinical Investigation* Peters et al. report studies in the transgenic hypertensive rat TGR(mREN2)27, a novel experimental model of hypertension that was derived by the transgenic expression of a mouse renin gene (Ren-2^d) on the genetic background of noninbred Sprague-Dawley rats (3, 4). The creation of this transgenic hypertensive rat was an impressive accomplishment and it is likely that the model will be useful for a variety of purposes, including pharmacologic studies, drug testing, and the investigation of blood pressure control mechanisms. But can these kinds of transgenic models provide any insight into the pathogenesis of spontaneous forms of hypertension?

Although the transgenic hypertensive rat clearly demonstrates that overexpression of the mouse renin gene in a Sprague-Dawley rat can give rise to increased blood pressure, the relevance of this model to natural forms of spontaneous hypertension remains uncertain. At first glance, it might seem predictable that overexpression of the renin gene would cause increased blood pressure and that the model would provide no more insight into the pathogenesis of spontaneous forms of hypertension than would hypertensive models produced by renal artery clipping or by continuous infusions of angiotensin II. In the transgenic hypertensive rat, however, the mechanism of increased blood pressure has not proven to be immediately obvious. This model is characterized by low levels of plasma renin activity and decreased renin gene expression in the kidneys. Thus, the hypertension does not appear to be simply caused by increased activity of the circulating or renal renin-angiotensin systems.

A striking feature of the transgenic hypertensive rat is the markedly increased expression of the mouse renin gene in the adrenals. Peters and colleagues have shown that adrenal expression of the mouse renin transgene gives rise to considerable adrenal secretion of active mouse renin (3). The release of active renin by the adrenals would be expected to generate increased local concentrations of angiotensin II, a well-known stimulus for adrenal steroid production. Peters and colleagues have also found that in adrenal cell suspensions from the transgenic hypertensive rat, angiotensin II further stimulates the release of active mouse renin thereby setting the stage for a positive feedback loop between renin release and angiotensin II (3). Given these observations and the fact that transgenic hypertensive rats exhibit increased urinary excretion of glucocorticoids and mineralocorticoids, the model may largely involve a form of steroid hypertension secondary to the excessive adrenal production of angiotensin II (4, 5). Nevertheless, the model would effectively demonstrate that a Mendelian form of increased blood pressure can result from disordered regulation of the renin-angiotensin system outside of the kidneys.

The concept that tissue renin-angiotensin systems outside of the kidney might contribute to some forms of high blood pressure has attracted enormous interest. However, in animals other than the transgenic rat, it has been difficult to demonstrate the secretion of active renin by tissues other than the kidney. Thus, the role of extra-renal tissue renin-angiotensin systems in the pathogenesis of hypertension continues to be highly controversial. While the transgenic hypertensive rat may demonstrate that overexpression of the renin gene in the adrenals or in other nonrenal tissues can give rise to hypertension, the question remains as to whether such phenomena are relevant to the pathogenesis of any form of spontaneous hypertension.

To the extent that transgenic models reveal novel mechanisms of increased blood pressure, they may provide important new perspectives for investigating the genetic basis of spontaneous forms of hypertension. However, the development of gene targeting methods that enable the creation of animal models with selective nucleotide substitutions will ultimately be required to determine the precise role of specific candidate genes in the pathogenesis of essential hypertension.

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