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Preventive Role of Renal Kallikrein–Kinin System in the Early Phase of Hypertension and Development of New Antihypertensive Drugs

Recent progress in hypertension therapy allows us to select appropriate drugs from the large variety of antihypertensive drugs for treating hypertensive patients, once hypertension is diagnosed. Antihypertensive drugs include angiotensin I converting enzyme (ACE) inhibitors, diuretics, calcium entry blockers, β-adrenergic receptor antagonists, α_1-adrenergic receptor antagonists, centrally acting α_2-adrenergic receptor stimulants, and so forth. It may be said that we are hardly in need of any more drugs against hypertension. Most of these drugs, however, are used for "therapeutic purposes" to suppress the symptoms of hypertension by mitigation of the increased vascular tone. We do not have any prophylactic drugs, since neither the primary cause nor the pathogenesis of essential hypertension has yet been properly identified, despite intensive research on the mechanisms involved in its development.

ACE inhibitors are among the most effective antihypertensives. However, studies over a period of years on the genetic and environmental determi-

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nants of hypertension, lipid abnormalities, and coronary artery disease in Utah in population-based multigenerational pedigrees (Williams *et al.*, 1993) and related investigations revealed that the genetic loci for the structural genes for renin (Williams *et al.*, 1993) and ACE (Jeunemaitre *et al.*, 1992a) and the sodium antiport system (Lifton *et al.*, 1991) were not DNA markers for hypertension.

In contrast, segregating single-gene effects were found for several "intermediate phenotypes" associated with hypertension, including intraerythrocytic sodium levels (Hasstedt *et al.*, 1988a), erythrocyte sodium-lithium countertransport (Hasstedt *et al.*, 1988b), and total urinary kallikrein excretion (Berry *et al.*, 1989). Furthermore, an important gene-environment interaction was found between urinary kallikrein and potassium intake (Hunt *et al.*, 1993a,b; Williams *et al.*, 1993). These studies on the genetic determinants of hypertension indicate that the renal kallikrein–kinin system may play an important role in the development of hypertension.

Many reviews on the renal kallikrein–kinin system in relation to hypertension have been published (Levinskey 1979; Carretero and Scicli, 1980, 1990; Mayfield and Margolius, 1983; Scicli and Carretero, 1986; Margolius, 1989). A more recent review on the roles of the kallikrein–kinin system in human diseases, particularly in hypertension, has also been published (Margolius, 1995).

A vasoactive polypeptide, bradykinin (BK), has been recognized as a potent vasodilating substance. A part of the hypertensive effect of ACE inhibitors was claimed to be attributable to the vasodilating activity of BK, because ACE inhibitors inhibit degradation of BK. As for the roles of the kallikrein–kinin system in the body, it is still too early to claim that entire features of this system and its roles have been clearly established, despite great research efforts and a considerable accumulation of knowledge. A major reason may lie in the difficulty of detecting BK in the blood and other biological fluids because of the extremely rapid destruction of BK (half-life: $\sim$ 17 sec) in the blood. This difficulty can probably be overcome by the detection of a rather stable metabolite of this peptide in biological fluids. The other chief reason that the roles of the kallikrein–kinin system in the body have not been clarified resides in the difficulty of complete elimination of this system from the body. A recent trend toward the use of knockout mice may open the door to an understanding of the roles of the kallikrein–kinin system, but hypertension studies with knockout mice have not progressed. In the same context, a mutant strain of rats, Brown Norway–Katholiek (BN-Ka) rats, which have no kininogens in the blood and hence cannot generate kinins (see Section II.C), may be a very useful model for studying the role of the kallikrein–kinin system in the body, particularly in the development of hypertension, since they may be considered natural knockout rats.