Pathogenesis of Hypertension: A Review

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Hypertension, with a prevalence of up to 30% throughout the world, is increasing in incidence in more affluent and aging populations. Because it is totally asymptomatic, it has been named the "silent killer," as it is the major contributor-or risk factor-to cardiovascular morbidity and mortality. A large body of research over the past several decades has been devoted to investigating the causes and mechanisms of hypertension. Although the causes-genetic and environmental-remain obscure, much progress has been made in elucidating some of the pathogenic mechanisms causing hypertension, as well as its common complications, ie. ischemic heart disease, stroke and renal failure. The ultimate goal of this research is to inhibit these mechanisms and thus prevent or reverse the hypertensive complications.

Most prominent among these mechanisms are the renin-angiotensin system (RAS) and salt. Renin was discovered at the end of the 19th century by Tigerstedt and Bergmann and the components of the RAS had been characterized earlier in the 20th century through the work of Braun-Menendez in Argentina and Page in the United States. However, there were doubts on the importance of the RAS in the pathogenesis of hypertension and common hypertensive complications, mainly because of failure to find a correlation between levels of renin or angiotensin II (Ang II) and levels of blood pressure. A series of experimental and clinical studies starting in the 1970's helped clarify this apparent paradox by demonstrating the reciprocal relationship between sodium balance and RAS status. It was proven that an activated RAS causes not only hypertension, but also severe tissue damage in vital organs and that blockade of the RAS - either via Ang II receptor antagonists or angiotensin-converting enzyme (ACE) inhibitors - can prevent or reverse end-organ damage.

It was shown that exogenous Ang II excess in experimental animals1 or endogenous Ang II stimulation in humans2 resulted in severe myocardial necrosis and scarring, as well as renal tubular necrosis leading to renal failure, not necessarily correlated to blood pressure levels. A parallel survey of a hypertensive population revealed that high-renin hypertensives had a significantly higher rate of cardiovascular complications than low-renin hypertensives.3,4 Further work elucidated the close reciprocal relationship between the RAS and salt - the other major mechanism of hypertension. It was shown that both a RAS-mediated vasoconstriction and a salt mediated mechanism contribute to development and maintenance of hypertension. Salt overload is associated with suppressed renin levels, but when salt is removed (via diuretic treatment and/or low-salt diet) the RAS becomes activated and partly offsets the benefits of diuretic therapy.5-7 At the time, the prevailing opinion was that salt-mediated hypertension was due to retention of fluid and expansion of intravascular fluid volume (despite evidence of contracted...
blood volume and increased peripheral vascular resistance in most low-renin patients). However, subsequent experimental studies reconciled these findings by demonstrating that sodium excess stimulates initially vasopressin and later the sympathetic nervous system, which sustains the peripheral vasoconstriction. Therefore, the salt-dependent hypertension may indeed be "volume expanded" in terms of extracellular (but not intravascular) fluid volume, but is still characterized by increased arteriolar resistance.

Later experimental and clinical work demonstrated that interference with mechanisms of sympathetic activation at various levels, including pharmacologic sympathetic blockade, as well as genetic engineering or gene treatment to obliterate selected adrenergic pathways, can totally abolish the hypertensive response to excessive salt loading, both acute (infused parenterally) and chronic (dietary). This provided a final proof that the mechanism of salt-dependent hypertension is vasoconstriction due to sympathetic excitation and not hydrostatic pressure due to expanded plasma volume - which should not be surprising, as conditions with documented expanded plasma volume without salt retention, such as the syndrome of inappropriate antidiuretic hormone (SIADH) release, are characterized by hemodilution but not elevation of systemic blood pressure.

The elucidation of RAS-mediated mechanisms for the pathogenesis of hypertension and end-organ hypertensive damage, such as ischemic heart disease, heart failure, renal failure and stroke, was soon followed by development of therapeutic approaches to prevent or reverse these conditions. The earliest studies demonstrating therapeutic benefits of RAS blockade in hypertension and heart failure were conducted with pharmacologic probes given parenterally, such as the Ang II antagonist saralasin and the ACE inhibitor teprotide. The encouraging results of these pioneering studies led the pharmaceutical industry to develop first orally active ACE inhibitors and later, orally active Ang II type 1 receptor blockers (ARBs). Both these classes of drugs have now become recommended standard therapy for hypertension, heart failure, ischemic heart disease, chronic kidney disease (particularly diabetic nephropathy) and cerebrovascular disease. A vast number of long-term randomized clinical outcome trials have provided ample evidence that ACEI-based or ARB-based therapy can prevent, reverse or at least decelerate the progression of cardiovascular morbidity and diminish mortality.

In parallel, significant progress has been made in the elucidation of sodium triggered mechanisms for the pathogenesis of salt-induced hypertension. It has now been demonstrated that acute or chronic salt-excess alters the function of the \( \alpha_2 \) adrenergic receptors (ARs) in the central nervous system. The data suggest that elimination of the sympatho-inhibitory \( \alpha_2A-AR \) subtype or activation of the sympatho-excitatory \( \alpha_2B-AR \) subtype leads to hypertension. Conversely, activation of the \( \alpha_2A-AR \) subtype has a hypotensive effect and elimination of the \( \alpha_2B-AR \) subtype abolishes the hypertensive response to salt-loading. These more recent findings have not yet produced practical therapeutic approaches for selective treatment of the hyperadrenergic state that characterizes certain forms of hypertension, decompensated heart failure, coronary disease, arrhythmias, autonomic imbalance, etc. Nevertheless, a better understanding of the role of specific AR-subtypes in the pathogenic mechanism of these conditions should eventually lead to development of appropriate therapeutic interventions, as excessive dietary salt intake is probably the most important environmental factor causing hypertension in people who either are genetically salt sensitive or become so as a consequence of aging.

References
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