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Recent Advances in the Understanding of the Causes and Therapy of Essential Hypertension

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Abstract

Cardiovascular diseases have been recognized as one of the leading causes of death in North America. Hypertension is one of the very common form of cardiovascular diseases. It is estimated that one out of four North Americans is suffering from hypertension. Although this disease has been extensively studied for many decades, over ninety percent of the cases of hypertension are still considered as essential hypertension, meaning that the cause of the elevated blood pressure is unknown. It is now generally accepted that essential hypertension is a symptom of underlying disease state which is heterogeneous in origin. Thus far, only an overactive renin-angiotensin system (RAS) has been shown to be related to high blood pressure. This, however, can only account for approximately fifteen percent of the cases of essential hypertension. The cause(s) of the majority of cases remains unknown in spite of tremendous research efforts. Salt sensitivity is a correlate with about thirty to forty percent of hypertensives who have low renin activity in the blood. To identify the cause(s) of essential hypertension especially in salt-sensitive, low-renin patients is, therefore, an important area of basic and clinical research.

Calcium is an important ion in our body. It is known to be closely involved in the mechanism of smooth muscle contraction. Excessive contraction of vascular smooth muscle can increase peripheral vascular resistance and hence the elevation of blood pressure. It is known that cells of hypertensive animals and patients often contain higher levels of calcium than do cells of normotensive counterparts. In the past decade or two, there have been reports suggesting that high dietary calcium intake can reduce high blood pressure, especially in individuals that are salt sensitive and have low plasma renin activity. Such hypertensive animals and individuals also have higher cellular calcium concentrations. This is indeed a paradox which has perplexed the imagination of researchers. During the last five years, my laboratory has worked towards the understanding of such a paradox.

It was discovered that salt-sensitive and low renin animals and patients have in their circulation a higher level of a new vasoconstrictor which is unique in having a slow or delayed vasoconstricting effect when assayed in the normotensive rat. The origin of this factor is the parathyroid gland and it has been named the parathyroid hypertensive factor (PHF). The mechanism of action of PHF has been elucidated. It opens a specific type of calcium channels on the cell membrane of vascular smooth muscle cells (VSMC), thus increasing the intracellular calcium concentration $[Ca^{++}]$. The abnormally high $[Ca^{++}]$ does not necessarily cause overt vasoconstriction but sensitizes the VSMC to other circulating vasoconstrictors such as norepinephrine, arginine vasopressin and angiotensin. Since PHF

originates from the parathyroid gland which is known to be inhibited by calcium, a high calcium diet in salt sensitive animals and patients reduces the plasma levels of PHF. These findings provide a logical explanation for the paradox of why a high calcium diet can reduce high blood pressure despite the fact that $[Ca^{++}]$ is abnormally high. Our consequent investigations with animals and human suggest that PHF is a causative factor of salt-sensitive hypertension. These findings, therefore, have significant implications. Our studies not only provide a logical answer to a long existing paradox, but also led to the discovery of the cause of thirty to forty percent of the cases of essential hypertension.

Based on our understanding that PHF opens calcium channels, it is logical that calcium antagonists which block calcium channel activity, are effective in the treatment of essential hypertension. On the other hand, a high calcium diet is effective in reducing the plasma level of the causative factor, PHF. Although it seems illogical, theoretically a combination of calcium antagonist and high calcium diet should provide a synergistic effect in the treatment of this type of essential hypertension. The calcium antagonist would work at the site of action of the vasoconstrictor, and the high calcium diet at reducing the production of PHF. Experiments were designed to test the effect of such a combination therapy and the results showed, in hypertensive rats, the combination produced a striking synergistic and predictable antihypertensive effect. It seems that the discovery of PHF may provide an explanation of the calcium paradox, an understandable cause of salt-sensitive, low renin hypertension and also a rational approach to the treatment of such patients. As in many biomedical during the elucidation of this paradox and the subsequent discovery of the etiology of this specific type of hypertension.

Shake a full kettle, It will not rattle; But what a racket you can get, With a half-filled kettle! - an old Chinese Proverb