POINT/COUNTERPOINT

Insulin and Hypertension: Introduction

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A relationship between insulin and hypertension emerged in epidemiologic studies reported in the mid-1980s. The association of insulin with hypertension was most pronounced in obese hypertensive subjects but was noted in lean hypertensives as well. Although insulin is a direct vasodilator, it is also known to stimulate the sympathetic nervous system and promote renal sodium reabsorption, both potential mechanisms that might exert a prohypertensive effect. The observations that normotensive relatives of hypertensive patients demonstrate insulin resistance and the absence of insulin resistance in patients with secondary forms of hypertension both contributed to the possibility that insulin plays a role in the pathophysiology of essential hypertension. For these reasons, the relationship between insulin and blood pressure has blossomed into an area of considerable interest over the last decade. Multiple sessions devoted to this topic are common at national and international hypertension meetings. Debate at these sessions is, moreover, characteristically high spirited.

The actual role played by insulin in the pathogenesis of hypertension remains obscure. Definitive evidence of a causal role for insulin in initiating or maintaining essential hypertension in humans is lacking. Circumstantial evidence, on the other hand, abounds. In this Point/Counterpoint review, two authorities working in the field present their view of this relationship. Professor Hall and his colleagues have argued persuasively that experimental evidence, much of it from their own laboratories, does not support a role for insulin. Much of this experimental work, however, depends upon studies performed in the dog, and its relevance to human hypertension remains, therefore, problematic. Inferences drawn from patients with insulinoma (who lack hypertension) may be overstated since in insulinoma elevated insulin levels consist, at least in part, of proinsulin, and blood glucose levels tend to be low, rather than slightly elevated as they are in insulin-resistant subjects without insulinoma. If both insulin and glucose are involved in the prohypertensive process, this lower level of glucose might be an important distinguishing feature between patients with insulinoma and insulin resistant subjects with hypertension.

Professor Mark and his colleagues have demonstrated sympathetic stimulation in normal human subjects over and above what can be accounted for by the vasodilatory effects of insulin and have further defined, in experimental animals, areas of the central nervous system that respond to insulin and stimulate central sympathetic outflow. In their judicious consideration of the evidence, they raise the interesting possibility that subjects vary in their hypertensive response to insulin, thereby drawing a compelling analogy with salt sensitivity and resistance.

My own point of view is that insulin is involved in the pathogenesis of hypertension in some patients. This involvement reflects, I believe, the close physiological association between circulatory and metabolic regulation. Metabolic substrates need to be carried to and from appropriate organs for synthesis, storage, and utilization. Energy production, moreover, needs to be coupled with dietary intake and nutritional status. These metabolic processes, and the delivery and distribution of substrate, are orchestrated, in large part, by the sympathetic nervous system. Insulin may,

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therefore, play a critical role at the interface between metabolic and circulatory regulation. This relationship between insulin and the sympathetic nervous system may, in the organism predisposed by genetic or environmental influences, result in hypertension. As pointed out by Professor Mark, the fact that insulin resistance and hyperinsulinemia are not invariably associated with hypertension is not surprising; many factors are usually required to produce an elevation of blood pressure. The argument here is that insulin may exert a prohypertensive effect, which elevates the blood pressure in predisposed individuals. The epidemiologic evidence suggests that this group may comprise a substantial subset of hypertensive subjects.

Clearly more work needs to be done to clarify the importance of this intriguing relationship between insulin and hypertension. These two points of view, presented by expert investigators in the field, may help to define the issues and serve to focus subsequent investigation.