Hypertension

Sodium and the kidney: the non-modulator concept

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Introduction

In the late 1960s, Professor Gordon Williams and I, in independent, studies made observations that were to occupy us for the next 35 years of our scientific lives [1,2]. I identified a subset of patients with essential hypertension in whom renal blood flow did not follow shifts in salt intake. Dr Williams identified a group of patients in whom the adrenal aldosterone release in response to a reduction in salt intake was blunted. Because his interests in angiotensin-mediated control of the adrenal and my parallel interest in the control of the renal circulation were essentially identical, we decided to join forces in a collaboration that has continued for over three decades.

Sodium renal handling

Modulation

Our first advance came from our identification of a normal control mechanism [3]. On a high-salt diet in normal individuals, blood pressure but especially the renal vascular response to angiotensin II (AngII) was increased compared with responses on a low-salt diet. Conversely, the adrenal response to AngII was up-regulated on a low-salt diet. Because others had made parallel observations on the influence of glucose and insulin on the responsiveness of the insulin receptor—and used the term ‘modulation’ to describe those relationships—we used an identical term for the adrenal and renal responses, on the premise that a similar mechanism might be involved. It was. We then rather quickly recognized that his blunted adrenal responses and my anomalous renal responses occurred in the same patients, and reflected their inability to modulate normally; hence, the development of the term ‘non-modulation’ [4].

Non-modulation

In view of the fact that renal haemodynamics and aldosterone represented factors 1 and 2 in the control of renal sodium handling, it was reasonable to explore the influence of non-modulation on renal sodium handling. The effects were substantial [5–7]. Whether one employed the renal response to a short-time saline infusion or the response to sustained shifts in dietary salt intake, the responses of non-modulators differed from normal and from responses in other hypertensives. Non-modulators cannot handle a salt load normally, excrete the load more slowly, and thus are prone to salt-sensitive hypertension. Specifically, the rise in blood pressure associated with a shift from a low-salt to a high-salt diet in non-modulators is identical to that found in patients with low-renin essential hypertension, a syndrome widely recognized to be salt-sensitive [8,9].

The early studies were performed during the birth of approaches for pharmacological interruption of the renin–angiotensin system. We quickly learned that treatment with an ACE inhibitor would correct the renal and adrenal abnormality in non-modulators [5]. In the case of the kidney, the renal vasodilator response to ACE inhibition in non-modulators on a high-salt diet was essentially identical to the change in renal blood flow on a shift from a low to a high-salt intake in normal individuals. Normal individuals and other hypertensives, conversely, showed little or no renal vasodilator response to ACE inhibition on a high-salt diet. Treatment with an ACE inhibitor also rapidly restored the capacity of the kidney to handle a salt load [7], and corrected the hypertension. This provided an explanation for the paradox that these patients were both salt-sensitive and responsive to blocking the renin–angiotensin system. Low-renin hypertensives, conversely, are equally sensitive to salt intake, but are resistant to the antihypertensive effect of ACE inhibitors. In a follow-up study, the ‘ESPRIT Study’ [10], patients were enrolled in a therapeutic trial of the ACE inhibitor, lisinopril, as sibling pairs. The vast majority of the sibling pairs were non-modulators. With that entry criterion,
92% of Caucasians showed a significant response or reached goal blood pressure with ACE inhibition, with blood pressure measured by ambulatory blood pressure monitoring. Black patients received higher doses, and showed a smaller response.

Concerning the mechanisms responsible for non-modulation, a powerful clue came from examination of family history, as indicated above [6]. The vast majority of non-modulators have a strong family history of hypertension. Moreover, in physiological studies in sibling pairs, the renal response to AngII in the first sibling predicted strikingly response in the second [11,12]. In more recent genetic studies, we have shown that a polymorphism involving the angiotensinogen (AGT) gene at codon-235, individuals homozygous for threonine at that locus were non-modulators [13]. In follow-up studies on the adrenal response, neither the ACE gene nor the aducin gene independently predisposed to non-modulation, but both gene polymorphisms predisposed to a blunted adrenal response when associated with the AGT gene polymorphism.

A series of recent studies have suggested that non-modulation is associated with increased cardiovascular risk. Non-modulation is associated with microalbuminuria [14], with increased sodium and lithium counter-transport [15], and with insulin resistance [16]. What is primary and what is secondary in these relationships remains unclear, but as all are responsive to ACE inhibition [5,7,10,15], the findings suggest a pathogenetic final common pathway with angiotensin as an important contributing factor.

Surprisingly, even the increase in sodium: lithium counter-transport that occurs in non-modulators is reversed by ACE inhibition [15]. Families of patients with non-modulation show an increase in overall cardiovascular risk [9].

Conclusions

Taken in all, the findings suggest that non-modulation is a genetically determined syndrome with important implications for metabolism, cardiovascular function, and cardiovascular risk. We need a simple marker to identify these patients if we are to perform the appropriate large-scale epidemiological studies that are now necessary to prove this assertion.

References