

## Kallikreins, kinins and cardiovascular diseases: A short review

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*Studies of kallikrein-kinin systems since the 1930's have now led to substantial insight into the importance of this vasoactive system in the regulation of cardiovascular and renal function. It now seems clear that before long, these insights will lead to new therapeutic attacks upon diseases of the cardiovascular system and kidneys. This survey of notable recent work also emphasizes the fact that few of these fascinating new findings would have been produced without the stimulus of the initial discoveries of Héctor R Croxatto.*

**Key terms:** bradykinin, cardiovascular diseases, hypertension, kallikreins, kinins, spontaneously hypertensive rats

### INTRODUCTION

The contributions of Héctor R Croxatto to the study of vasoactive hormones, to the knowledge of what we know and what we still need to know about cardiovascular and renal function and diseases, have been matched by very few biomedical scientists. His sort of devotion, energy and –most notably– enthusiasm for biomedical research and the joy of discovery are found only rarely in the scientific world. Much of what we know about kallikreins, kinins and cardiovascular diseases is a result of his ability to not only make discoveries, but to communicate clearly the potential for greater meaning in his findings. It is more than notable that even his most recent work is characterized by not only “solid science”, but also the capacity to provoke and surprise (Croxatto *et al*, 1997). It is a privilege and an honor to participate in a celebration of his achievements.

### EARLY HISTORY

The early history of kallikrein-kinin systems begins at the turn of the century when two French biologists discovered the vasodilator properties of mammalian urine (Abelous & Bardier, 1909). The characterization of kallikrein, the entity responsible for this property, took almost twenty years (Frey & Kraut, 1928), and several more years to determine that kallikrein was an enzyme and could be quantitated (Werle, 1936), as well as found to be abnormally reduced in the urine of patients with hypertension (Elliot & Nuzum, 1934). Despite a rapid confirmation of the results of Elliot and Nuzum by Frey, Werle and colleagues, and an extension of the finding of reduced urinary kallikrein excretion to diabetic subjects as well, this seminal work was ignored by scientists interested in hypertensive or metabolic diseases for

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more than thirty years. These early events occurred just as Croxatto was beginning his career contributions to the study of hypertension and the role of the kidney.

In 1970, this author finished clinical training at the Harvard Medical Services of the Boston City Hospital and began a fellowship with Dr Albert Sjoerdsma, Chief of the Experimental Therapeutics Branch of the National Heart and Lung Institute in Bethesda, Maryland. Dr Sjoerdsma, the preeminent American clinical pharmacologist, directed a program focussed upon hypertensive disease mechanisms and discoveries of potential relevant to new therapies. He said: "Harry, look around for something that interests you and get to work". This attitude, coupled with a level of extraordinary judgement about the capabilities of young biomedical scientists, had created an environment full of outstanding people and important discoveries. It was also fun to work there.

I soon fell in with Drs John Pisano, Marion Webster, Jack Pierce and Vida Beaven. They, and a visiting Norwegian scientist, Kjell Nustad, were attacking various biochemical aspects of kallikrein-kinin systems, including tissue kallikrein purification from rat kidney, kininogen purification from human plasma, identification of components of the plasma kallikrein system, and attempts to create new assays for kinin system components. Pisano was a brilliant and innovative chemist, who was able to also focus a significant portion of his substantial intellect upon the practical application of his biochemical interests to human disease. His contributions to clinical chemistry had already, especially in the area of catecholamine metabolism, become highly valued. He suggested I try to help Dr Beaven establish an assay for kallikrein in human urine, a task she had abandoned earlier because of unpredictable recoveries of the purified enzyme from human urine samples. In rather short order, we solved the problem, and I was able to begin to measure the levels of kallikrein in the urine of normal volunteers, patients with essential hypertension, or forms of secondary

hypertension, such as pheochromocytoma or primary aldosteronism.

At the time, advice was freely available from some senior colleagues who suggested, sometimes quite strongly, that I was, "risking my scientific investment" by working on something that nobody was interested in, rather than renin and angiotensin, catecholamines, or steroid hormones. Nevertheless, our initial results were very exciting, as we found that urinary kallikrein levels were significantly reduced in the primary disease, and markedly elevated in the two forms of secondary hypertension. Sjoerdsma, returning from a short sabbatical in the fall of 1970, then allowed us to enlist the further help of Drs Ronald Geller (who was already performing bioassay determinations of human urinary kallikrein levels) and Wybren de Jong, a visiting Dutch pharmacologist. They were to help in an attempt to extend the clinical findings into the spontaneously hypertensive rat, a colony of which had recently been established at Bethesda, the DOCA-salt hypertensive rat, as a model for the humans with primary aldosteronism, and finally the two-kidney, one-clip renal hypertensive rat, because de Jong had great skill in placing these partially occlusive slips on rat renal arteries.

It is difficult to recollect precisely the factors responsible for the acceleration of our excitement as the weeks rolled by. However, in the preparation of the first paper on the work, a short communication to the *Lancet* (Margolius *et al*, 1971), I found, (after Marion Webster mentioned one day that she was sure someone had done some such thing, many years earlier), the work of Elliot and Nuzum mentioned above. This "library discovery" served as a focus for our first communication, and provided a life-long reminder to me, as a young, ambitious, and not particularly sensitive, scientist, to pay a bit more attention to the literature. In beginning to do so, I then found the paper of most importance to my subsequent life in science.

In the above mentioned paper, Croxatto and San Martin (1970) showed the disappearance of kallikrein from the urine of renal hypertensive rats. Although their

most dramatic results were seen in the one-kidney hypertensive animals, their findings, and the discussions amongst us in Bethesda that followed, served to solidify our commitment to the study of kallikreins, kinins and hypertension. It is still a pleasure to read this contribution (my copy is a bit yellowed but still quite legible), and its' conclusion that kallikrein-like activity in the urine "is inversely correlated with arterial blood pressure", and "it is possible to assume that kallikrein in the urine reflects the kidney impairment which leads to the renal hypertension development". For us to see this data as we were embarking upon our own work, was a stimulus only rarely encountered. Their data told us that what we were thinking about and doing had value, perhaps even importance, but in the main, it meant we should "endeavour to persevere" in our work. Now, in what seems like "the blink of an eye", almost thirty years have passed, those early findings have been confirmed many times over, and the promise evident in the study of kallikrein-kinin systems is widely recognized as likely to have profound importance to the treatment, and perhaps even prevention, of cardiovascular, renal and metabolic diseases.

#### STUDIES IN HUMAN HYPERTENSION AND CARDIOVASCULAR CONTROL

Today, interest in possible kallikrein-kinin contributions to the pathogenesis of human hypertension is growing rapidly because of a series of provocative findings reaching from epidemiological surveys to gene-polymorphism-cosegregation analyses (Pravenec *et al*, 1991). Many studies of hypertensive populations show abnormalities in kallikrein excretion (Margolius, 1989). Black people, adults and children, excrete markedly less kallikrein than whites, regardless of blood pressure, with black hypertensive subjects generally showing the lowest measured levels (Zinner *et al*, 1976; Levy *et al*, 1977). In recent years, studies of kallikrein and other system components in some more homogeneous human populations have

begun to appear. For example, Japanese patients with low-renin hypertension show significant reductions in both active urinary kallikrein and kinin excretion (Nakahashi *et al*, 1986). They also demonstrate higher levels of a kallikrein inhibitory material in urine and reduced urinary kininogen and increased urinary kininases. In other studies, urinary kininase excretion including kininase I, II and neutral endopeptidase 24.11 was measured in patients with primary aldosteronism and it was found that total, kininase I, and neutral endopeptidase levels were elevated in these patients, with return of all abnormal levels into the normal range in one patient studied before and after removal of the tumor (Ura *et al*, 1995). Gainer *et al* (1996) noted that African Americans are at an increased risk for ACE inhibitor-associated angioedema and therefore evaluated the wheal response to intradermal bradykinin in salt-replete, hypertensive and normotensive African Americans and Caucasians. They found that African American race and the presence of hypertension were associated with an increased wheal response to bradykinin, providing additional support for racial differences in the kallikrein-kinin system and further implication of system abnormalities in essential hypertension. Studies such as these are now providing a stimulus for exploration of system component genotypes in relationship to phenotypic characteristics of hypertensive populations. A particularly notable new review of the role of the renal kallikrein-kinin system in hypertension and the possibility of new drug development based upon studies of the system has appeared recently (Katori & Majima, 1996).

Some of these studies of kinin system components and roles are in populations of patients not primarily characterized by their hypertensive status. In a large scale study of insulin-dependent diabetic patients, Marre *et al* (1997) have shown that the severity of the nephropathy associated with the disease was strongly associated with an angiotensin converting enzyme (kininase II) insertion/deletion polymorphism, but not directly linked to other known polymorphisms of the renin-angiotensin

system such as in angiotensinogen, or angiotensin receptor. Thus, there is a genetic determinant that probably affects renal angiotensin II and kinin levels, which also can affect systemic blood pressure and the progression to renal failure in patients with diabetes. Work such as this compels further examination of other candidate genes such as those of the kininogens, kallikreins and kinin receptors for polymorphisms which may be linked to the predilection for hypertensive disorders.

In addition, the potential for other roles for tissue kallikrein and its kinin product in human cardiovascular homeostasis and disease is expanding rapidly. Knock and Poston (1996) have carried out a particularly provocative study of human arterial vascular reactivity in small arteries obtained from biopsy specimens at cesarean section from 24 normotensive pregnant women, 6 with preeclampsia, and during abdominal surgery from 15 nonpregnant women. Arteries from the normotensive pregnant women demonstrated enhanced relaxation to bradykinin compared with arteries from nonpregnant women but the relaxation response was blunted significantly in the vessels from women with preeclampsia. The response in all groups was mediated by nitric oxide with an increase in vessels from the pregnant normal women and a relative reduction in the preeclamptic population. The work provides some support for the notion of kinin-mediated control of vascular resistance. Further support comes from the work of Groves *et al* (1995), who infused icatibant (HOE140) into the left main coronary artery of 15 patients undergoing routine diagnostic coronary arteriography. After HOE140, there was a significant reduction in luminal area in proximal, mid and distal vessels. There was also a significant reduction in flow-dependent dilation and the work demonstrated for the first time, a seeming role for endogenous kinin in mediating vasodilator responses in the human coronary circulation.

Another very interesting contribution is that of Kuga *et al* (1995), who examined the effect of bradykinin on vasomotion of epicardial coronary arteries in patients with

normal coronary arteries, patients with organic coronary stenosis, and patients with vasospastic angina. Changes in the diameter of arteries were assessed with quantitative arteriography. They found that the kinin can produce vasodilation of these vessels, but such is impaired at atherosclerotic sites but not at vasospastic sites of patients with this type of angina. Studies such as this, and that of Hornig *et al* (1997) are leading to a greater appreciation of the possible contributions of endogenously generated kinin to vascular wall behavior. In the latter study, high resolution ultrasound and Doppler measurements of blood flow velocity were used in healthy volunteers to measure radial artery diameter and blood flow. It was found that neither angiotensin-converting enzyme inhibition with quinaprilat or the kinin B2 receptor antagonist icatibant (HOE140) affected basal arterial diameter or blood flow. However, icatibant reduced significantly flow-dependent dilation, and the increase seen after quinaprilat alone was reduced to the same extent by co-infusion with icatibant, as with icatibant alone. This work indicates that the accumulation of endogenous kinin has a role in the vascular effects of angiotensin-converting enzyme (kininase II) inhibitors in humans.

This brief survey of some recent clinical work reaffirms that there are still many questions left to be explored concerning the roles for kallikreins and kinins in human cardiovascular diseases.

#### STUDIES IN HYPERTENSIVE AND OTHER ANIMAL MODELS

The number and novelty of new approaches to the study of the role of tissue kallikrein-kinin system activity in animal models is increasing rapidly. In part, this is due to the description of animal models not previously available, as well as to the larger community of scientists world-wide, with interest and technology for assessment of system activity. For example, Campbell *et al* (1995) measured tissue bradykinin and kinin metabolites at several sites including

kidney, adrenal, lung, heart and brain in young spontaneously hypertensive (SHR) and control rats and found increased kinin levels in the first four sites in the SHR. Kinin levels were similar in the two strains in aorta, fat and brain. Although the significance of the differences is unclear, the association of these abnormalities with this genetic hypertensive strain even before the appearance of hypertension, provides several questions for study.

Majima and colleagues (1993) have made significant advances by studying the Brown Norway Katholiek (kininogen-deficient) rats. These animals display a rapid increase in blood pressure when fed a 2% NaCl diet at 7 weeks of age. A subcutaneous infusion of low molecular weight kininogen caused a significant reduction in blood pressure, along with increased urine volume, sodium and kinin levels whereas infusion of icatibant or aprotinin induced a hypertensive response. These results suggest that the lack of kinin generation in these kininogen-deficient rats might be responsible for the hypertensive response to NaCl loading. In another study (Majima *et al*, 1994), 7 week old animals were given angiotensin II (20 µg/d sc) for two weeks via an osmotic minipump. The kininogen-deficient animals showed a large increase in blood pressure two weeks later, from  $132 \pm 2$  mm Hg to  $181 \pm 5$  mm Hg, but no increase occurred in the control rats. Additional experiments showed that kininogen infusions decreased the blood pressure, heart rate and erythrocyte sodium levels in the angiotensin II-infused animals. The mechanisms responsible for the noted changes still need further exploration but probably include hormonal contributions (*e.g.*, aldosterone) as well as other direct or indirect actions of the peptides, yet to be clarified.

In this regard, it is clear that the extent of interaction between angiotensin and bradykinin are yet to be fully understood. Paula *et al* (1995) have shown that the hypotensive response to bradykinin in conscious rats is potentiated by the administration of angiotensin 1-7, a metabolite of angiotensin II that is increased in plasma and tissue after

administration of converting enzyme inhibitors. In essence, the 1-7 metabolite is a bradykinin-potentiating peptide *in vivo*, whose mechanism of action is being clarified by some extraordinary discoveries about the activities of converting enzyme by Erdos and his colleagues (in press, 1998). In other studies, Gohlke *et al* (1997) have found that endogenously generated kinin appears to be responsible for the ACE-inhibitor-induced increase in cardiac capillary length density observed in stroke-prone SHR, treated prenatally and up to 20 weeks of age with ramipril. This very interesting study showed that while the development of hypertension or left ventricular hypertrophy was unaffected by chronic kinin B2 receptor blockade, the effects of low-, or high-dose ramipril to increase capillary length density were abolished by icatibant (HOE140). The role of a local kallikrein-kinin system, or blood-borne kinins in this striking phenomenon remains to be studied.

Further evidence for a kinin contribution to cardiac muscle survival is found in the study of Schrieffer *et al* (1996), who used inhibitors of endopeptidases 24.11 and 24.15 to determine if ischemia/reperfusion injury of rabbit heart was kinin mediated. In their work the significant protective effect of the inhibitors was blocked by icatibant (HOE140) and enzyme assays demonstrated that the endopeptidases were present in the rabbit heart. This work is confirmed in principle by the study of Liu *et al* (1996) in which it was shown that the protective effect of converting enzyme inhibition against ischemia/reperfusion injury and arrhythmias in rats was mediated by a kinin-prostaglandin-nitric oxide pathway which could be blocked by HOE140, indomethacin or L-NAME, but not by the angiotensin II receptor blocker, losartan.

Additional work has used other animal models or found new sites and actions of kallikreins and kinins. Mutant mice lacking bradykinin B2 receptors were found to show a significantly higher blood pressure in response to a long-term high salt diet than control mice (Alfie *et al*, 1997). In addition, the receptor knockout mice had reduced renal blood flow and a

doubled renal vascular resistance, suggesting that kinins play a role in the prevention of salt-sensitive hypertension. In addition, to such confirmation of much older suggestions, there are observations opening entirely new areas of study. Privitera and Yates (1995) have found that microinjections of tissue kallikrein in the rostral ventrolateral medulla of brain increased blood pressure in both Wistar-Kyoto and spontaneously hypertensive rats but significantly more in the SHR and this paradoxical effect was blocked by HOE140. The role of central kallikreins and kinins in blood pressure homeostasis requires still more study.

Jaffa *et al* (1997) recently found that diabetic rats demonstrate reduced renal kallikrein mRNA and kallikrein protein levels, and that both insulin and IGF-1 could increase kallikrein mRNA and protein levels, but at higher IGF-1 doses than required in control rats. Thus, diabetes not only suppresses renal kallikrein (and renin) gene expression, which can be reversed by insulin or IGF-1, but the diabetic state produces an interesting resistance to IGF-1 induction of kallikrein gene expression. Another example of work basic to our eventual understanding of the roles of tissue kallikreins and kinins is the study of Wang *et al* (1996), in which an understanding of the effects of bradykinin upon endothelial cells, to augment microvascular junctional patency is sought. They have found that the kinin causes redistribution of an endothelial cell cytoskeletal protein called filamin from the peripheral cell border to the cytosol of confluent cells. This occurs subsequent to an increased cytoplasmic calcium, activation of a calcium/calmodulin-dependent protein kinase signalling pathway, and results in increased vascular junctional permeability by releasing filamin from F-actin. This translocation of filamin appears to be an early step in the eventual loss of intravascular fluids and macromolecules to the interstitial space. Studies such as these allow the raising of many questions of eventual relevance to human cardiovascular homeostasis and diseases.

#### NEW QUESTIONS, OPPORTUNITIES AND THERAPEUTIC POTENTIAL

The last thirty years of work on kallikreins, kinins (and other relatively unappreciated proteinases and peptide hormones), has now led us to an enormously expanded number of questions about the roles of such enzymes and their products in cellular, tissue and organism homeostasis and disease. It is suggested that a reading of even a few of the above mentioned new studies will reinforce this conclusion, at least to the student of the subject still willing to ask questions, unafraid of failure, and ready for the unexpected. As a final example, it is easy to pick another recent contribution from the work of Croxatto and another talented colleague (Boric & Croxatto, 1995) which as usual provides a convincing, but surprising result. In this work it was shown that the diuretic, natriuretic and kaliuretic actions of atrial natriuretic peptide (ANP) in anesthetized rats, were antagonized by prior administration of bradykinin in doses which themselves had no effect upon basal urinary output. This effect of the kinin was prevented completely by the kinin B2 receptor antagonist, HOE140. A similar blunting of the natriuretic and diuretic action of ANP by the converting enzyme inhibitor, ramipril, was also blocked by HOE140 allowing the conclusion that intrarenal kinins can actually antagonize the effects of ANP. This is the sort of work one has come to expect from Croxatto and colleagues, which continues to raise interesting possibilities, and compel the conclusion that important insights into physiology, disease pathogenesis and new therapeutic strategies and tactics, are yet to come from the follow-up of his discoveries.

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