Role of inflammatory cells in the kidney in the induction and maintenance of hypertension

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\textsuperscript{1}Two forms of inflammation can be separated from one another; the purely parenchymatous inflammation, where the process runs its course in the interior of the tissue… and the secretory (exudative) inflammation where an increased escape of fluid takes place from the blood… Every parenchymatous inflammation has from its outset a tendency to alter the histological and functional character of an organ\textsuperscript{.} Rudolf Virchow (1860).

**Introduction**

The incidence of hypertension has increased dramatically in the last decade [1]. While the relative importance of environmental, congenital and genetic factors have been extensively debated, there is a general agreement that, whatever the cause, there is a
dysfunction in the mechanisms responsible for sodium excretion by the kidney [2]. Not surprisingly, a reduction in dietary sodium is one of the time-honoured mainstays of all antihypertensive regimes.

Recent attention has been focused in the renal accumulation of inflammatory cells in hypertensive conditions and its relation with local oxidative stress and angiotensin II activity [3]. This interrelationship is critical in the development of sodium retention and represents an example of what Rudolf Virchow defined, more than a century ago, as the functional alterations induced by 'parenchymatous' inflammation [4].

The present editorial will discuss current evidence that links the accumulation of immunocompetent cells in the kidney and a pathophysiologic state of sodium retention that can initiate and maintain arterial hypertension.

**Inflammatory cells in the kidney in human and experimental hypertension**

The data of the association of renal inflammatory infiltration and hypertension is relatively scarce in humans; however, early [5] as well as recent data [6] indicate that arteriolar disease and tubulointerstitial mononuclear cell infiltration are prominent features of hypertensive nephropathy. Conversely, the association of interstitial nephritis with hypertension has been well documented in chronic pyelonephritis, hyperuricaemia, analgesic nephropathy, cyclosporin nephrotoxicity and potassium depletion [7–10]. Macrophage and lymphocyte infiltration have been noted in the DOCA-salt model of hypertension, two-kidney one-clip Goldblatt hypertension, aortic coarctation, low-level lead intoxication, Page (cellophane-wrap) hypertension, hypokalaemic nephropathy, hyperuricaemia, renal injury from catecholamine or angiotensin II infusion, nitric oxide synthase (NOS) inhibition, protein overload nephropathy [reviewed in 3], as well as in two different genetic strains of hypertensive rats [11,12]. More importantly, the administration of mycophenolate mofetil (MMF), which reduces the immune cell infiltration (in addition to significant antiproliferative effects on mesangial and smooth muscle cells) results in a significant improvement of hypertension in spontaneously hypertensive rats (SHR) [13] and other models [14] or in the prevention of the salt-sensitive hypertension induced following angiotensin II infusion [15], L-NAME administration [16] or intraperitoneal BSA administration [17].

The renal infiltration of immune cells is an early event that precedes the development of hypertension in the SHR [18], which is an important finding because stimulation of pro-inflammatory factor nuclear factor-kappa B (NF-κB) is an expected effect of reactive oxygen species (ROS) [19] and increased oxidative stress may be the result as well as the cause of hypertension [20]. Furthermore, early and sustained inhibition of NF-κB is associated with long-term normal blood pressure in the SHR [21].

**Sodium retention as an expected result of intrarenal inflammation**

The sodium retention induced by tubulointerstitial inflammation is linked to two conditions that are unavoidably associated with intrarenal inflammation: increased local (intrarenal) angiotensin II activity and increased oxidative stress.

Angiotensin II reduces sodium excretion by both glomerular and tubular effects. Angiotensin II may lead to a decrease in the ultrafiltration coefficient $K_f$ and single nephron glomerular filtration rate, which would result in a decrease in the filtered sodium load, while the more distal effects of angiotensin II include a stimulation of proximal sodium reabsorption and impairment of pressure diuresis. Relevant to the present discussion, intrarenal angiotensin II functions as an isolated compartment, unresponsive to systemic haemodynamic changes and is actually increased by a high-salt diet [22]. Several lines of evidence indicate that intrarenal angiotensin II is increased as a result of interstitial inflammation. First is the demonstration that the tubular epithelial cells and infiltrating cells in the kidney express angiotensin II in experimental models of hypertension [12,15–17]. Second is the observation that glomerular haemodynamic changes similar to those induced by angiotensin II are present in salt-sensitive hypertension experimental models [23]. Third is the finding that renal angiotensin II content is increased in interstitial nephritis [14] and, finally, that the treatment with MMF, which reduces the accumulation of immune cells, reduces the number of angiotensin II-positive cells and prevents the angiotensin II-driven glomerular haemodynamic alterations [23].

Systemic increase in oxidative stress is associated with arterial hypertension [24]. Within the kidney, ROS induce vasoconstriction by direct and indirect (impaired vasodilatation by inactivation of endothelial nitric oxide, inhibition of vasodilatory PGI2 and increased intracellular calcium) mechanisms promoting increased sodium reabsorption [18]. Furthermore, ROS-induced microvascular damage, particularly in peritubular areas, impairs pressure natriuresis [25].

The cross-stimulation between oxidative stress, angiotensin II activity and interstitial inflammation is complex and intense. Tubulointerstitial inflammation generates oxidative stress and increased angiotensin II activity and both these conditions result in local NF-κB-mediated inflammation in the kidney.

**General overview of the pathogenesis of hypertension in relation to intrarenal inflammation**

In previous communications we have suggested that essential hypertension could follow in two stages: an early salt-resistant stage, characterized by a preserved autoregulation of glomerular circulation and a salt-sensitive stage characterized by a change in slope
Persistent intrarenal ischaemia as a consequence of increased expression of CD18 adhesion molecules [27]. CD8 and CD4 lymphocytes, the latter demonstrating peripheral blood monocytes and by an infiltration with increased hydrogen peroxide production by drive in the kidney. In fact, hypertension is associated which, in turn, may keep a non-specific inflammatory pathophysiology drives sodium retention.

Intrarenal inflammation and arterial hypertension. Immune and non-immune renal conditions associated with arterial hypertension present intrarenal inflammation that supports and is supported by the generation of oxidative stress and local angiotensin II generation. The resulting glomerular and tubular ischaemia as a consequence of structural changes in the vasculature (luminal narrowing of the pre-glomerular arterioles and peritubular capillary rarefaction) and pre-glomerular vasoconstriction could also lead to a persistent inflammatory response. At this time there are no human data that directly address these potential mechanisms for persistent inflammation. Furthermore, most experimental studies from which insights may be derived have used anti-hypertensive treatments, such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor type 1 blockers (ARB) that also have significant anti-inflammatory activity which confounds interpretation.

Alternatively, we have raised the possibility that low-grade inflammation in tubulointerstitial areas of the kidney could be maintained by autoimmune reactivity [6].

**Questions for the future**

Compelling evidence indicates that oxidative stress, intrarenal angiotensin II activity and interstitial inflammation are intricately linked in the hypertensive kidney [3]; therefore, it is reasonable to consider the potential benefits of a multiple approach to the treatment of arterial hypertension.

First, normalization of blood pressure levels with other antihypertensive drugs should not preclude the need of suppressing the renin–angiotensin system. Indeed, protection of end-organ damage by ARBs is not dependent on blood pressure reduction [28]. Yet, there are practical difficulties in determining the usefulness of this approach. Since massive proteinuria is not a characteristic of essential hypertension, the potential benefit of therapies aiming at blocking the renin–angiotensin system could not be monitored by the reduction in urinary protein excretion. Furthermore, suppression of intrarenal angiotensin may require regimes that combine ACE inhibition and ARBs that carry additional hazards, such as hyperkalaemia and anaemia [29]. Nevertheless, inhibition of an overactive intrarenal angiotensin system is expected to reduce proinflammatory mediators and superoxide generation, which should complement the haemodynamic benefit of lowering the blood pressure.

It may also be worthwhile to explore the possible benefits of additional antioxidant and anti-inflammatory treatment in the hypertensive patient. Several large trials have already attempted to evaluate the effects of antioxidant treatment in hypertension and while the results have been, in general, disappointing [30], problems in the design, drug choice and evaluation of the achieved antioxidant effects are largely unresolved [3,30]. Finally, in specific instances, it may be worthwhile to consider if treatments directed to reduce the interstitial immune cell accumulation could have additional short- or long-term benefits. These approaches represent exciting theoretical possibilities that, in our view, merit bench-side
investigation to define their potential benefit in the hypertensive patient.

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