Hypertension-induced renal injury: is mechanically mediated interstitial inflammation involved?

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Introduction

Volhard and Fahr [1] recognized that hypertension per se causes renal damage and described the renal pathology. In patients with malignant hypertension, renal failure is an expected event; in patients with less severe forms of hypertension chronic renal failure also occurs, albeit at a lower frequency and to a lesser degree. The interplay between hypertension, renal disease progression, and the mechanisms by which hypertension damages the kidneys are not known for certain; however, the processes are so intertwined that consideration of one without the other is hardly possible. The glomeruli have been a focal point of interest, particularly with the hyperfiltration hypothesis involving the degradation and sclerosis of terminal nephrons [2]. However, the notion that tubulointerstitial fibrosis may be the cause of decreased glomerular...
function rather than the effect, has recently received strong support [3]. We shall draw attention to the less orthodox aspects of hypertension-induced renal injury.

Patients with essential hypertension do not routinely undergo diagnostic renal biopsy. Thus, our knowledge of hypertension's impact as a cause of chronic renal failure and our understanding of the human pathology is limited. Our information stems from observations of animal models. These models are as heterogeneous, as the human condition is likely to be. Our interest has focussed on two-kidney one-clip (2K1C) renovascular hypertension, which induces a severe form of renal injury that has fascinated students of the hypertensive kidney since Wilson and Byrom [4]. Instead of a predominantly glomerular injury, we found perivascular monocytic infiltration, an expansion of the interstitial volume, and interstitial accumulation of matrix collagens, laminin, and fibronectin [5]. The cell proliferation did not take place in the glomeruli, but rather in the tubules. Interstitial macrophage and T lymphocyte infiltration was a prominent event, which occurred before the matrix proteins were deposited.

The renal interstitium is just not a passive space in which the truly functional renal units reside. Rather, it is a highly dynamic tissue in which structural support is rendered, fibers and ground substance are produced and degraded, substance exchange and lymphatic drainage are provided, and hormonal functions are conducted. The recruitment of inflammatory cells, cytokines, proliferation of fibroblasts and matrix deposition within the interstitium may be key events in the fibrotic process accompanying all chronic renal diseases. Thus, a careful consideration of inflammatory responses, the participation of cytokines and growth factors, and a central role for the renal interstitium may be relevant in the pathogenesis of hypertension-induced renal injury as well.

**Microvascular injury**

Inflammatory changes featuring perivascular infiltrates of monocytes and macrophages occur in hypertension-induced vascular injury [6]. Wilson and Byrom held extravasation of plasma protein components into the vessel wall to be responsible [4]. We also found that perivascular macrophages and monocytes were a prominent early feature of 2K1C hypertension [5]. The role of macrophages, as a source of chemotactic and multifunctional pleiotropic cytokines, may be pivotal. Macrophages may also proliferate locally under these circumstances. In hypertrophic hearts from spontaneously hypertensive rats, we observed not only macrophage infiltration, but also expression of c-fms, the proto-oncogene coding for the macrophage colony stimulating factor receptor [7]. Expression of c-fms exceeded that of c-myc and c-sis, proto-oncogenes which express transcription factors involved in hypertrophy. Conceivably, similar events occur in the kidney exposed to hypertension.

Endothelial cells lining the vessel wall are the first cells exposed to the increase in blood pressure. They respond with functional and structural alterations to the altered conditions. Vasoactive substances released from endothelial cells, such as endothelin may contribute to the vasoconstriction observed in these vessels. In addition, endothelin may play a role in the activation of infiltrating macrophages [8]. A second feature of endothelial cell dysfunction is the increased expression of surface adhesion molecules. In our model of 2K1C hypertension expression of the adhesion molecule ICAM-1 was observed very early in the disease. The increased expression of ICAM-1 was associated with an accumulation of LFA-1 positive leucocytes, suggesting that ICAM-1 was responsible for the recruitment of these cells.

Post-glomerular vessels are particularly involved in hypertension-induced and other forms of renal damage [9]. In the rat remnant kidney model, tubular cells express PDGF, especially when blood pressure is not controlled [10]. Mechanical stretch of vascular smooth muscle cells is also capable of causing the cells to express PDGF. This potent mitogen for interstitial fibroblasts and vasoconstrictor substance may be partly responsible for the rarefaction in post-glomerular blood vessels observed in progressive renal disease. The net result and functional consequence would be tubular hypoxia and injury.

**Tubular cells and the interstitium**

Tubular cells showed early evidence of injury and proliferation in our model of 2K1C hypertension [5]. Tubular toxicity is intimately involved in interstitial injury and filtered proteins, ischaemia, or both may be involved. Protein in the luminal fluid when metabolized by proximal tubular cells yields a chemotactic factor which has activity for macrophages [11]. Proximal tubular cells are also capable of antigen presentation. Macromolecular antigens may arrive on the apical surface of the proximal tubular cells following filtration. These antigens can be subsequently delivered to the basolateral surface, where they may activate T helper cells. T lymphocytes were also prominently present in our model [5].

Ischaemia of tubular cells induces an early increase in class I antigens in the tubular epithelial cells and a later increase in class II antigens in interstitial cells [12]. Proximal tubular cells can also produce surface adhesion molecules, specifically ICAM-1, which facilitates interaction with T lymphocytes. ICAM-1 interacts with the LFA-1 ligand on leukocytes that fosters adhesion of T cells to antigen-presenting cells. Interferon-gamma, IL-1, and TNA-alpha, perhaps elaborated by macrophages, can all act to promote surface adhesion molecule expression on tubular cells.

Thus, such non-immune vascular processes could lead to non-immune tubular cell injury, which could in turn foster activation or expansion of normal, resident, immune cells and promote the influx of new
cells, initially in response to tubular derived cytokines such as MCP-1 and IL-8. Class II antigen expression and ICAM-1 expression by tubular cells would be augmented further through the secretion of lymphokines, enabling tubular cells to present more antigen. Neoantigens could be filtered proteins or antigens on tubular cells exposed by ischaemia.

Collagens I, II, IV, V, VI, laminin, and fibronectin appeared in the interstitium of our rats early in the course of their 2K1C hypertension (5). In contrast, the glomerular matrix was not involved in this process. Tubular cells may synthesize collagens IV and V normally and under abnormal conditions may also elaborate collagens I and III. However, fibroblasts are the usual source for collagens. Rodemann and Müller have suggested that a fibroblast with altered phenotype may develop in chronic renal disease [13], possibly in response to protein-induced renal injury.

Conclusion

Hypertension not only causes pre-existing chronic renal disease to progress more quickly, but causes chronic renal disease as well. The primary feature of this process appears to be interstitial injury, in part 'inflammatory interstitial nephritis', if you will. The changes involved occur in the microvasculature, include obstruction of the post-glomerular interstitial capillary network, intimately involve the proliferation of renal tubular cells, eventually result in tubular atrophy, cause interstitial inflammatory cell infiltration and culminate in interstitial fibrosis. The glomeruli may participate by allowing an increased capillary permeability to macromolecules and other proteins. This framework (Figure 1) is admittedly incomplete; however, it provides the beginnings of an explanation for the paradox of 'mechanical' events which lead to immunological injury.

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References