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Review Articles

Microscopic Changes in the Hypertensive Heart and Kidney – Structural Alterations, Role of Mast Cells and Fibroblast Growth Factor-2

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Hypertension is among the disorders with the highest impact on human health and healthcare systems around the world. It is responsible for various pathological conditions, which lead to a shortened life expectancy. There are multiple studies on the effects of prolonged hypertension on the heart and kidneys. While much is known about the structural and functional changes occurring in the left ventricle, data exploring the alterations in the right ventricle are quite scarce. In this review article, we report on the structural alterations in both ventricles and in the kidney. We also present newly emerging evidence on the role of mast cells and fibroblast growth factor-2 in hypertension-induced fibrosis in the heart and kidney. The aim of this review is to look at some recent scientific data and point out the role of often overlooked aspects of hypertensive heart and kidney damage, which may well turn out to have a pivotal role in the better understanding and treatment of these conditions.

Key words: Mast cells, fibroblast growth factor-2 (FGF-2), heart, kidney, hypertension, spontaneously hypertensive rats (SHR)

Introduction

Hypertension is a worldwide disease, which is recognised as an important risk factor for premature death. Prolonged and untreated hypertension is a major reason for the development of inevitable structural alterations in many organs and systems, which are collectively described by the term ‘target organ damage’. The most commonly affected organs are heart, kidneys and brain, and the most common hypertension-related disorders include coronary heart disease (CHD), end-stage renal disease (ESRD) and stroke, respectively. Elevated blood pressure leads to an increased hemodynamic stress

on the myocardium, thus causing myocardial remodelling first evident by changes in the myocytes at the ultrastructural level. Historically, those changes have been well evaluated for the left ventricle (LV), but changes in the right ventricle (RV) have often been overlooked. An increasing number of recent studies have been assessing the pathological changes and dysfunction of the RV and their relation to the LV. In the kidney, hypertensive damage is related to renal fibrosis in both the medulla and cortex caused by expansion of extracellular molecules. Scientific evidence demonstrates that changes in the interstitial tissue correlate better with renal function than changes in the glomeruli [35]. Recent reports have indicated that damage found in these target organs is associated with the pathological function of mast cells, well beyond their previously explored role in allergic and anaphylactic reaction, as well as signal molecules expressed by them, such as fibroblast growth factor-2.

Herein, we report on the structural alterations in both ventricles and in the kidney. We also present newly emerging evidence on the role of mast cells and fibroblast growth factor-2 in hypertension-induced fibrosis in the heart and kidney. The aim of this review is to look at some recent scientific data and point out the role of often overlooked aspects of hypertensive heart and kidney damage, which may well turn out to have a pivotal role in the better understanding and treatment of these conditions.

Structural changes in the hypertensive heart

It is a well known fact that prolonged hypertension leads to microstructural and functional changes in the heart. The spontaneously hypertensive rat (SHR) is an often used model of hypertensive target organ damage. Blood pressure in this animal reaches systolic values of 180-200 mmHg as early as 4-6 weeks of age, with subsequent alterations observed in their heart, kidneys and other target organs [18,27,29]. These changes have been shown to correlate with changes observed in human organs. Therefore, it should be noted that a significant number of studies focusing on the structural aspects of hypertensive damage are based on this animal model.

CHD and its complications are responsible for a considerable burden on healthcare systems around the world. Hypertension is among the leading factors for the development of CHD. The chronic increase in hemodynamic stress causes myocardial remodelling and is associated with alterations at the ultrastructural level. A study by Iliev et al. showed similar ultrastructural changes in both the LV and RV [10]. The progression of hypertensive heart damage is accompanied by cardiomyocytic hypertrophy, hypertrophy and hyperplasia of the cardiomyocytic nuclei and multiple invaginations of the nuclear membrane. Alterations in the strict arrangement of the myofibrils, with occurrence of disorganised filamentous structures adjacent to the myofibrils are also observed. In addition, it is noted that mitochondria become swollen, with appearance of amorphous matrix and disintegration of the cristae. These changes take place along with an increased collagen deposition in the interstitial space, as evidenced by the presence of multiple fibroblasts and the development of endo- and perimysial fibrosis [10].

Structural changes in the hypertensive kidney

Many cases of newly diagnosed ESRD are due to hypertension-induced damage and the structural changes in the kidney associated with it. The relationship between hypertension and ESRD is pathologically referred to as hypertensive nephrosclerosis.

Alterations occur in both the interstitium and parenchyma. They include changes such as glomerulosclerosis, thickening of the glomerular basement membrane, tubular atrophy of distal and proximal segments, hyaline and fibrinoid arteriosclerosis and proliferation of the intimal smooth muscle cells of the interlobar arteries [32,34]. Glomerular injury can be classified in two types: solidification and obsolescence, each presenting with a definitive ultrastructural picture. The alterations, in the solidification type, are represented by collapse of the glomerulus and intracapsular fibrosis. Distinctive changes in the obsolescence type include expansion of the matrix and enlargement of the glomeruli tuft [34]. Interstitial fibrosis can be observed throughout the kidney structure – periglomerular, peritubular, periarteriolar fibrosis. It is associated with expansion of the extracellular matrix [32].

The role of mast cells and FGF-2 in the hypertensive heart

Another interesting finding in the hypertensive heart is the presence of mast cells. Mast cells are well known mononuclear cells, which participate in the innate immune response of the body. They take part in the regulation of multiple physiological functions and also play a main role in pathological conditions such as allergies, anaphylactic shock, etc. There are two types of mast cells, which have been described in rats. These are mucosal mast cells (MMCs) and connective tissue mast cells (CTMCs). Both types differ in lifespan, localization and dependence on T cells [8]. MMCs are found in the intestinal and respiratory mucosa. CTMCs are found around blood vessels and nerve endings. MMCs are T-cell induced and T-cell dependent, while CTMCs are T-cell independent [8]. MMCs contain chymase in their granules, while CTMCs contain chymase, tryptase and carboxypeptidase [16].

The presence of CTMCs has been described in the LV of the heart [19,26]. Recent studies have demonstrated the role of these cardiac mast cells in the pathogenesis of myocardial remodelling in the LV [11,17,19]. In particular, the essence of the mediators contained in mast cell granules – namely chymase, tryptase, histamine, fibroblast growth factor-2 (FGF-2), transforming growth factor-beta (TGF-beta) – have been discussed. These mediators initiate the activation and proliferation of fibroblasts, the differentiation of myofibroblasts and collagen synthesis [17,19]. Mast cell granules also contain tumour necrosis factor-alpha (TNF-alpha), which is responsible for promotion of apoptosis of the cardiomyocytes, hypertrophy, inflammation and increase in the expression of matrix metalloproteinase-9. In addition, the stem cell factor (SCF) and its receptor on the mast cell membrane c-kit (also known as CD117), have been shown to have a role in the survival, proliferation, differentiation and maturation of mast cells. SCF, in particular, is important for the interaction between fibroblasts and mast cells [2,3]. Interestingly, mast cells can produce SCF themselves, which may signify possible autoregulation [3]. Anti-inflammatory cytokines, such as interleukin-10 (IL-10) and interleukin-33 (IL-33) produced by mast cells are another factor demonstrating their complex role in heart remodelling [15,17]. Mast cells are involved in both myocardial remodelling after myocardial infarction and in heart failure, and fibrotic remodelling caused by hypertension and myocarditis [20].

An interesting recent finding by Iliev et al. is the presence of mast cells not only in the LV, but also in the RV of SHR [10]. Moreover, a comprehensive study by Kotov et al. discovered that a statistically significant increase in the number of mast cells takes

places as hypertensive heart damage progresses. The authors also used a semi-quantitative analysis to evaluate FGF-2 immunoreactivity in the myocardium of the LV and RV, and demonstrated an increase in the expression of this growth factor in both ventricles as hypertension progressed [15]. The same study reported a positive correlation between the number of mast cells, the expression of FGF-2 and the extent of interstitial fibrosis in both ventricles [15]. These findings further solidify the data from previous studies on the connection between mast cells and interstitial fibrosis [12,21]. The information above can be demonstrated by the following cascade: increase in mast cells → increased synthesis of FGF-2 by mast cells → increased collagen production and interstitial fibrosis → further stimulation of mast cells by fibroblasts through the SCF-c-kit pathway [15]. Perhaps contrastingly, Widiapradja et al. observed that what increases is not the actual number of mast cells, but rather the percentage of mature mast cell, showing the need for more studies in the area so it can be fully understood [43].

The role of mast cells and FGF-2 in the hypertensive kidney

Another target organ which is impacted by the prolonged elevation of blood pressure is the kidney. With time, hypertension leads to renal injury and changes in the structure of the kidney, which ultimately causes ESRD. Morphological changes affect both the renal parenchyma and interstitium and include glomerulosclerosis, arteriolar sclerosis, tubular atrophy, infiltration of inflammatory cells and expansion of the extracellular matrix [23]. An interesting fact demonstrated by numerous studies is that changes in the interstitium rather than these in the glomeruli are more indicative of the extent of kidney damage and correlate better with renal function [30,40]. A recent research by Stanchev et al. showed that it is the various cellular interactions which lead to the above-described changes rather than a simple accumulation of molecules in the interstitium [37].

Similar to the heart, more recent data have focused on the role of mast cells and FGF-2 in the development of interstitial changes in the kidney [28,33]. Researchers observed that renal damage, regardless of its pathological origin, is accompanied by an increase in the number of mast cells in the kidneys, as well as SCF levels. Furthermore, the number of mast cells also increases with the extent of kidney damage [41,42]. In number of pathological conditions mast cells localise in the interstitium around vessels and tubules but are not found in the glomeruli [42]. A recent work by Stanchev et al. found a similar picture in the kidneys of SHR – namely, the lack of mast cells in the renal corpuscles [33]. As previously mentioned, FGF-2 is an important growth factor released by mast cells, which leads to proliferation of mesangial cells, glomerular and tubular epithelial cells, vascular endothelial cells and vascular smooth muscles. In their study, Stanchev et al. observed a positive correlation between the immunoreactivity of FGF-2, the number of mast cells and the degree of tubulointerstitial changes [33]. While FGF-2 levels in the corpuscles were minimal, other studies have described positive expression of FGF-2 in the layers of the Bowman's capsule and the glomerular mesangium [5,38].

Renal fibrosis is a complex process. A balance exists between collagen synthesis and collagen degradation. Many studies revealed the close relationship between mast cells and fibroblasts [24,39]. Stanchev et al. found a possible correlation between mast cells and the extent of renal fibrosis – there was a higher number of mast cells in SHR with more advanced hypertension-induced renal fibrosis [33]. Significant evidence points to the fact that tryptase secreted by mast cells serves as a mitogen for fibroblasts responsible for collagen synthesis [7,14,33]. Myofibroblasts are another key element in

the development of renal fibrosis. It has been reported that they can serve as an indicator of the extent of renal extracellular expansion. Fibroblasts stimulated by mast cells can differentiate into myofibroblasts [6,22]. Mast cell-fibroblasts relationship, however, is a two-way relationship, with the latter capable of influencing mast cell differentiation and activation by producing SCF. It should nevertheless be noted that other studies have presented contradictory data. Kim et al. observed a decrease in collagen type I expression induced by mast cells [13], while Miyazawa et al. concluded that mast cells exhibit a renoprotective effect [24].

In line with the above data, it would be worth noting that the expression of various collagen types in the kidney changes in response to hypertension. Collagen types I, III and V are commonly expressed in the renal interstitium, while only type V is expressed in the glomeruli. Prolonged hypertension leads to glomerular injury and subsequent glomerulosclerosis. These processes are associated with an increased expression of collagen types I and III [35]. A research by Stanchev et al. also observed an increase in the expression of collagen type V in the parietal and visceral layer of the glomerular capsule of SHR, which suggests a possible role in the process of renal fibrosis [35]. While only collagen type V is expressed in healthy kidney glomeruli, in the process of glomerulosclerosis deposition of types I and III is noted in the glomerular capillary tufts [1,35]. Finally, the study of Farris et al. revealed a likely key role of myofibroblasts in renal fibrosis, revealing thus another aspect of the complex mechanism behind hypertension-induced kidney damage [4].

Conclusion

Hypertension-induced changes in target organs such as the heart and kidney are associated with multiple alterations at the ultrastructural level and are initiated and maintained by complex mechanisms. Notably, in contrast to earlier understanding, the RV of the heart appears to be affected in a similar manner to the LV, albeit to a lesser degree. Recent evidence suggests that mast cells and substances produced by them, in particular FGF-2, are implicated in the development of interstitial fibrosis in the heart and kidney in response to elevated blood pressure. The positive correlations between the number of mast cells, the expression of FGF-2 and the extent of cardiac fibrosis are a reliable foundation for future research. Similar correlations show that the higher number of mast cells and the stronger expression of FGF-2 are associated with more pronounced renal alterations as evidenced by changes in the respective markers of renal damage and fibrosis, further supporting the shared mechanism of hypertension-induced heart and kidney damage.

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