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Common pathophysiological mechanisms of chronic kidney disease: Therapeutic perspectives

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ABSTRACT

It is estimated that over 10% of the adult population in developed countries have some degree of chronic kidney disease (CKD). CKD is a progressive and irreversible deterioration of the renal excretory function that results in implementation of renal replacement therapy in the form of dialysis or renal transplant, which may also lead to death. CKD poses a growing problem to society as the incidence of the disease increases at an annual rate of 8%, and consumes up to 2% of the global health expenditure. CKD is caused by a variety of factors including diabetes, hypertension, infection, reduced blood supply to the kidneys, obstruction of the urinary tract and genetic alterations. The nephropathies associated with some of these conditions have been modeled in animals, this being crucial to understanding their pathophysiological mechanism and assessing prospective treatments at the preclinical level. This article reviews and updates the pathophysiological knowledge acquired primarily from experimental models and human studies of CKD. It also highlights the common mechanism(s) underlying the most relevant chronic nephropathies which lead to the appearance of a progressive, common renal phenotype regardless of aetiology. Based on this knowledge, a therapeutic horizon for the treatment of CKD is described. Present therapy primarily based upon renin–angiotensin inhibition, future diagnostics and therapeutic perspectives based upon anti-inflammatory, anti-fibrotic and hemodynamic approaches, new drugs targeting specific signaling pathways, and advances in gene and cell therapies, are all elaborated.

Contents

1. Introduction to chronic renal disease

Chronic kidney disease (CKD) is a life-threatening condition characterized by progressive and irreversible loss of renal function. The increasing inability of the kidneys to properly clear the blood of

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waste products eventually results in the implementation of dialysis (or kidney transplant) in order to prevent azotemia, systemic organ damage and death. Due to its high prevalence and associated mortality, CKD is an important human and social burden. It is estimated that over 10% of adults in developed countries suffer some degree of CKD (De Zeeuw et al., 2005; U.S. Renal Data System, 2005). Direct cost derived from the disease consumes up to ~2% of health care system budgets, the majority of which is consumed by only ~0.1% of the population receiving dialysis in developed countries (Excerpts from the United States Renal Data System, 2000; Xue et al., 2001; Winkelmayer et al., 2002; Szczech & Lazar, 2004; U.S. Renal Data System, 2009). CKD can result from a variety of etiologically distinct causes. Presently, diabetes and hypertension are the two leading causes of CKD, although infectious glomerulonephritis, renal vasculitis, ureteral obstruction, genetic alterations, autoimmune diseases and others are also common causes of CKD. However, as the disease progresses, a common renal phenotype develops regardless of the cause. In addition to addressing the cause, a greater knowledge of the pathophysiological mechanisms underlying the common progression of CKD may unravel new targets for pharmacological intervention. In this sense, animal models have emerged as important tools for understanding the mechanisms implicated in the pathogenic process, and also for the assay of prospective therapies.

2. Hypertensive nephropathy

Hypertension is the second leading cause of end-stage renal disease (ESRD). As an example, according to the United States Renal Data System (U.S. Renal Data System, 2009), about 51–63% of all patients with CKD are hypertensive. This number grows to 90% in patients over 65 years. In the corresponding general population the incidence of hypertension is 11–13% and 50%, respectively. Hypertension causes a nephrosclerotic glomerulopathy characterized by (i) renal vasculopathy affecting preglomerular arteries and arterioles, resulting mainly from atherosclerosis, endothelial dysfunction, wall thickening and fibrosis; (ii) microvascular disease of the glomerular tuft capillaries; (iii) diffuse glomerulosclerosis and, less often, focal and segmental glomerulosclerosis (FSGS), involving damage to the filtration barrier constituents (podocytes, mesangial cells and basement membranes); and (iv) interstitial fibrosis (Rosario & Wesson, 2006). Overall renal blood flow decreases as a consequence of arteriolar vasculopathy, vascular obstruction and decreased vascular density. However, GFR initially stays relatively constant. This is due to (i) increased glomerular capillary pressure resulting from deficient or upwardly reset renal autoregulation; and (ii) damage to the filtration barrier resulting in greater permeability. Subsequently, GFR decreases as a consequence of a progressive loss of surface area, mesangial hypertrophy and increasing glomerular and peritubular fibrosis. Concommitantly, basement membrane alterations produce albuminuria and protein hyperfiltration.

2.1. The hypertension-renal damage loop

Hypertension is a common outcome of CKD regardless of etiology, which contributes to the progression of renal damage. Approximately 40% of patients with stage 2 CKD (glomerular filtration rate, GFR: 60–90 ml/min per 1.73 m^2 of body surface), and virtually all in stage 4 (GFR: 15–29) or 5 (GFR: <15 ml/min per 1.73 m^2 of body surface) are hypertensive (Rosario & Wesson, 2006). Similarly, chronically hypertensive animals and humans develop CKD as a consequence of high blood pressure, which mechanically damages renal glomeruli and renal vessels (Wiederkehr et al., 2005). Hypertension-induced CKD can be also the consequence of non-mechanical damage (e.g. increased angiotensin II (ANG-II) or decreased NO). Epidemiological correlations between hypertension and renal damage can be interpreted in both ways. In fact, hypertension may arise from subtle renal lesions (arteriosclerosis and endothelial dysfunction) resulting from acquired (genetic) traits and environmental insults (Johnson et al., 2005a,b). Accordingly, nephropathy can also be viewed as a primary renal lesion that progresses in parallel to and initiates the rise in blood pressure. The multidirectional and complex relation among cardiovascular and renal disease, atherosclerosis, fibrosis and tissue hypoperfusion and ischemia, is reinforced by the fact that (i) all these conditions share common risk factors, and (ii) the same gene polymorphisms (e.g. of renin–angiotensin aldosterone system—RAAS-components) seem to be related to many (if not all) of them (Rosario & Wesson, 2006). A vicious circle is closed by renal damage, renal vascular disease and hypertension. Therefore, it is likely that entering the circle through any of these avenues ultimately generates and results in an indistinguishable pattern of disease.

A growing body of evidence suggests that hypertension arises from a renal vasculopathy initially affecting renal arteries, or from renal microangiopathy involving preglomerular arterioles that eventually causes preglomerular vascular dysfunction or maladaptive remodeling and intrarenal focal ischemic damage (Johnson et al., 2005a,b; López-Hernández & López-Novoa, 2006). Vasculopathies and microangiopathies may be (i) caused by genetic determinants; (ii) provoked by environmental insults; (iii) secondary to systemic conditions, like atherosclerosis or the metabolic syndrome; or (iv) derived from transient and intermittent fluctuations in blood pressure, which overtime slowly inflict progressive damage to intrarenal vessels (even in the presence of a good renal autoregulation; see below in this section). Such fluctuations may be derived from hyperactive sympathetic activity arising from diverse factors that include stress, exacerbated cold responses, type A personality, etc. (Johnson et al., 2005).

Clinical, epidemiological and experimental correlations between hypertension and renal microvascular disease (with or without relevant renal dysfunction) are strong (Goldblatt, 1947; Sommers et al., 1958; Tracy et al., 1986; Rodriguez-Iturbe et al., 2004; Johnson et al., 2005a). Ultimately, abnormal preglomerular resistance for any given level of blood pressure and skewed autoregulation alter the precise medullary blood flow that signals for the appropriate level of natriuresis and blood pressure, leading to hypertension (López-Hernández & López-Novoa, 2006), as Goldblatt envisioned about 60 years ago (Goldblatt, 1947). It is easy to postulate how alterations in a few glomerular vessels would be able to reset the whole renal function. Affected nephrons have modified endocrine profiles (e.g. renin secretion) that alter the function of healthy or mildly injured nephrons (Sealey et al., 1988). Then, hypertension-associated renal damage would paradoxically originate from renal damage itself or, more precisely, from subtle, focal renovascular damage, where hypertension would be another mere consequence acting as a magnifying amplifier in the vicious circle of malignancy.

2.2. Hypertensive nephropathy

In general terms, both genetic [e.g. spontaneously hypertensive rats (SHR; Camp et al., 2003); stroke-prone SHR (SHR-SP; Nakamura et al., 1996); fawn hooded hypertensive rats (FHH; Weichert et al., 2001); Lyon hypertensive rats (LHR; Sassard et al., 2003)] and induced [e.g. uninephrectomy (UNX) + DOCA salt (Kretzler et al., 1994), or L-NAME administration (Van Dokkum et al., 1998)] animal models of hypertension replicate most of the essential events associated with human glomerulopathies. Hypertensive animals usually develop a clear nephropathy with renal dysfunction biomarkers and histological alterations, starting with glomerulosclerosis and progressing to nephron degeneration and tubulointerstitial fibrosis, similar to the findings in human hypertensives (Kriz et al., 1998). An exception is observed with Milan hypertensive rats, whose age-dependent nephrosclerosis is less evident than in the Milan normotensive rat (Brandis et al., 1986; Menini et al., 2004). However, in general, animal models of hypertension and hypertensive renal