Renal Transplantation Studies in Genetic Hypertension

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Renal cross-transplantation experiments revealed that the kidney plays a key role in primary hypertension. Advanced animal breeding strategies leading to the generation of congenic and consomic rat strains combined with renal transplantation experiments will allow researchers to quantify the contribution of renal and extrarenal mechanisms to the development of genetic forms of hypertension.

Arterial hypertension is a major risk factor for the development of stroke, chronic heart failure, and end-stage renal disease. The prevalence of arterial hypertension in societies with a western lifestyle is ~15%. Within human populations, arterial pressure variability can be ascribed to familial and non-familial factors. About 60–70% of the familial aggregation of arterial pressure in humans is determined by genetic factors.

Quantitative analyses of physiological systems involved in arterial pressure regulation revealed that isolated changes in total peripheral resistance and/or cardiac output are not sufficient to induce sustained hypertension unless the renal capacity to excrete electrolytes and fluid at a given arterial pressure level is compromised simultaneously (10). Increased renal retention of sodium and fluid causes arterial pressure to rise, which restores body sodium and fluid balance via the pressure natriuresis and diuresis mechanism (10). These findings, which were the results of animal experiments and mathematical modeling, contributed to direct attention to renal physiology and pathophysiology in the field of hypertension research.

Various rodent forms of genetic hypertension have been established for experimental investigation of hypertension genetics and pathophysiology, including spontaneously hypertensive rats of the Okamoto-Aoki strain (SHR), Dahl salt-sensitive rats, Milan hypertensive rats, Lyon hypertensive rats, and Prague hypertensive rats. SHR have been the most frequently used experimental animals in research on genetics and pathophysiology of arterial hypertension. Several pathophysiological features of this rat strain are important for the understanding of human hypertension and for preclinical development of antihypertensive drugs.

Already at the age of 3–6 wk, the pressure natriuresis and diuresis relationship in these animals is shifted to elevated arterial pressure levels (17). Renal afferent arteriolar resistance and tubular sodium reabsorption is increased compared with normotensive animals, and a putative renal endocrine blood pressure-lowering mechanism is reset to elevated arterial pressure levels. These abnormalities in renal function are consistent with an involvement of renal mechanisms in the pathophysiology of hypertension in SHR.

In addition to intrarenal mechanisms, neuroendocrine factors may contribute to the development of arterial hypertension in SHR. Sympathetic nerve activity is elevated in this strain, and sympathetic innervation of several target organs develops faster and is more dense than in normotensive rats. Neurohumoral reactivity to environmental stress is enhanced compared with normotensive rats. Brief angiotensin-converting enzyme inhibition in juvenile SHR as well as neonatal interruption of peripheral sympathetic innervation chronically reduce arterial pressure associated with a reduction in peripheral vascular resistance (11, 14). These effects may be at least in part due to interference with renal development and function.

Renal cross-transplantation in rats with genetic hypertension

To investigate the contribution of renal mechanisms to the development and maintenance of genetic (primary) forms of hypertension, renal cross-transplantation experiments have been performed. This type of experiment requires genetically hypertensive and normotensive rat strains with good histocompatibility to avoid confounding effects of secondary hypertension due to chronic renal allograft rejection and/or immunosuppression.

It has been demonstrated in Dahl salt-sensitive rats (5), Milan hypertensive rats (1), and Prague hypertensive rats (12) that arterial hypertension can be transferred with a renal graft from either hypertensive strain to normotensive histocompatible recipients. Furthermore, renal grafts from the respective normotensive control strains lowered arterial pressure in these three genetically hypertensive rat strains. Thus it has been consistently shown that renal mechanisms play a major role in the maintenance of genetic forms of hypertension in rats.

Renal transplantation experiments in SHR

In the past, investigations on renal mechanisms in SHR genetic hypertension applying renal transplantation techniques have been more circumstantial than in other genetically hypertensive rat strains (1, 5, 12) because no histocompatible normotensive rat strain was available for cross-transplantation experiments (Fig. 1). Therefore, F1 hybrids (F1H_{SHR×WKY}) derived from intercrossing SHR and normotensive inbred Wis-tar-Kyoto rats (WKY) have been used as recipients for both SHR and WKY kidneys. F1H_{SHR×WKY} are heterozygous at all autosomal gene loci. Arterial pressure in these animals is significantly less than in SHR but somewhat elevated compared with

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WKY. Histocompatibility genes of both parental strains are coexpressed in these animals, allowing for transplantation of renal grafts from either parental strain. However, F1H(SHR × WKY) cannot be used as kidney donors for SHR recipients. When F1H(SHR × WKY) were transplanted with an SHR kidney and both native kidneys were removed, recipients developed arterial hypertension (13). Transplantation of an F1H(SHR × WKY) or WKY kidney into F1H(SHR × WKY) did not induce hypertension (6, 7, 13).

Mechanisms involved in the development of renal posttransplantation hypertension

Glomerular filtration rate and renal blood flow were similar in F1H(SHR × WKY) with a solitary kidney graft obtained from either SHR or WKY (6). Morphological examination revealed some interstitial mononuclear infiltration in both SHR and WKY kidney grafts attributable to ischemia and reperfusion injury. In SHR but not in WKY kidney grafts, thickening of the media in small- and medium-sized intrarenal arteries was observed.

A consistent observation of several experiments was increased renal sodium retention in recipients of an SHR kidney compared with controls transplanted with a WKY kidney associated with suppressed aldosterone secretion (6). Data on the renin-angiotensin system did not suggest that its activation is a major contributor to the development of renal posttransplantation hypertension in recipients of an SHR kidney. Plasma renin activity and plasma angiotensin-converting enzyme activities as well as plasma angiotensin I and angiotensin II concentrations were similar in recipients of an SHR and a WKY kidney (16). Intrarenal renin activity (13) as well as mRNA contents for renin, angiotensin-converting enzyme, and angiotensinogen (16) were almost identical in transplanted SHR and WKY kidneys.

Sympathetic reinnervation of SHR kidney grafts does not contribute to renal posttransplantation hypertension. Measurements of adrenal tyrosine hydroxylase mRNA contents and analyses of discharge characteristics of splanchic sympathetic nerves did not reveal sympathetic activation to be associated with hypertension in recipients of an SHR kidney (7). Responses of sympathetic nerve activity and arterial pressure to a centrally acting sympatholytic substance (7) did not provide evidence for elevated central sympathetic drive and increased dependence of arterial pressure on sympathetic tone in recipients of an SHR kidney (Fig. 2). Thus current data do not support the hypothesis that neurohormonal activation is of major importance for the development of renal posttransplantation hypertension.

In kidney donors and recipients, physiological systems involved in renal development and/or circulatory control can be manipulated by pharmacological treatment. Renal cross-transplantation between differentially pretreated animals with identical genetic backgrounds provides a means to investigate the interactions of renal and extrarenal physiological systems in long-term arterial pressure regulation and in the pathophysiology of renal posttransplantation hypertension.

FIGURE 1. Renal cross-transplantation between spontaneously hypertensive rats of the Okamoto-Aoki strain (SHR) and normotensive Wistar-Kyoto rats (WKY) is impossible due to major differences in histocompatibility antigens. In F1 hybrids (F1H(SHR × WKY)) derived from crossing SHR and WKY, histocompatibility genes (RT1\(^\text{k}\) and RT1\(^\text{l}\)) of both parental strains are expressed. These animals can be used as recipients for kidney grafts of either parental strain but not as donors for recipients of the parental strains. When F1H(SHR × WKY) are transplanted with an SHR kidney, they develop arterial hypertension.

FIGURE 2. Responses of mean arterial pressure (MAP), heart rate (HR), and mean integrated splanchic sympathetic nerve activity (SNA) to intracerebroventricular administration of the \(\alpha_2\)-adrenoceptor agonist guanabenz (GBZ) did not differ between recipients of an SHR kidney (●; \(n = 8\)) and recipients of an F1 hybrid (F1H(SHR × WKY)) kidney (○; \(n = 7\)). Data points represent averaged values recorded over 15 min in conscious, freely moving animals. Recording started 5 min after injections were completed (*\(P < 0.001\) vs. recipients of an F1H(SHR × WKY) kidney, ‡\(P < 0.05\) vs. control period) Reprinted from Ref. 7 with permission.
iology of hypertension. This strategy allows for interventions during early ontogenesis, and difficulties regarding chronic measurements of neurohumoral parameters in small rodents are avoided. This type of experiment also allows for studies of differential gene expression in the kidney without confounding effects of multiple genetic differences between donor and recipient strains unrelated to hypertension.

An important question regarding the role of the kidney in long-term arterial pressure regulation in SHR is whether arterial pressure can be lowered by a kidney graft from a genetically normotensive donor. An initial study (15) addressed this issue by performing renal allotransplantation. At the time of that study, no normotensive donor strain with the SHR haplotype of the major histocompatibility complex was available. SHR were either transplanted with an SHR kidney or they received a renal allograft. Native kidneys were removed in all animals, and treatment with an anti-CD4 antibody and cyclosporine was performed. The same treatment was administered to controls transplanted with a renal isograft. Reprinted from Ref. 15 with permission.

To exclude confounding effects of allograft rejection and immunosuppression on long-term arterial pressure, a normotensive histocompatible rat strain was established by a breeding strategy leading to congenic animals. These normotensive BB.1K rats are homozygous for a 2-cM segment of SHR chromosome 20, including the class Ia and class II genes of the SHR major histocompatibility complex, and allow for cross-transplantation experiments with SHR without the need for immunosuppression. We could demonstrate that a solitary BB.1K kidney transplanted into bilaterally nephrectomized SHR lowered arterial pressure to the level of the normotensive donor strain accompanied by improved renal sodium excretion and regression of left ventricular hypertrophy (8). These data indicate that renal mechanisms are central for the maintenance of arterial hypertension in SHR.

Renal transplantation and genetics of hypertensive renal disease

Besides investigations into the role of the kidney in primary hypertension, renal cross-transplantation techniques have been applied to study hypertensive renal damage. Hypertensive renal damage is a major contributor to morbidity and mortality associated with arterial hypertension irrespective of its etiology.

To examine the genetic determination of hypertensive renal damage, Kurtz and co-workers (2) used a congenic rat line derived from spontaneously hypertensive rats. These animals (SHR-RT1.N) harbor a 31-cM region of chromosome 20, including the genes of the major histocompatibility complex from normotensive Brown Norway rats, on an SHR genetic background. SHR-RT1.N were unilaterally nephrectomized and transplanted either with a kidney from Brown Norway rats or with an SHR-RT1.N kidney. Unilaterally nephrectomized SHR were transplanted with an SHR kidney. Severe secondary hypertension was induced in all groups by treatment with DOCA salt. Examination of native and transplanted kidneys revealed more severe glomerular and vascular damage in kidneys from Brown Norway rats compared with SHR and SHR-RT1.N kidneys when exposed to the same degree of arterial hypertension (2). These data indicate that the susceptibility to hypertensive renal damage in rats is genetically determined.

Renal transplantation and genetic hypertension in clinical medicine

In humans, end-stage renal disease can be caused by multiple factors, including diabetes mellitus, primary and secondary hypertension, glomerulonephritis, and tubulointerstitial nephritis. These factors may act in combination, complicating
the analysis of the etiology of end-stage renal disease in individual patients. The final therapy for these patients besides hemodialysis is renal transplantation.

After careful analyses, Curtis et al. (4) demonstrated primary hypertension as the cause of end-stage renal failure in six patients. These patients were bilaterally nephrectomized and transplanted with kidneys from normotensive donors. After an average follow-up time of 4.5 yr, these patients were found normotensive without antihypertensive medication despite immunosuppressive therapy (4). The arterial pressure normalization after transplantation of a kidney from normotensive donors was associated with regression of left ventricular hypertrophy and hypertensive retinopathy. Furthermore, renal handling of sodium was similar to normotensive controls in response to variations of daily sodium intake between 9 and 300 mmol (4).

Another study followed 85 patients with end-stage renal disease of different origin for an average of 8 yr after renal transplantation (9). All transplant recipients lived with at least one native kidney. Donors and recipients were grouped according to their family history of hypertension. The major finding of that study was that recipients with a negative family history of hypertension needed more antihypertensive treatment to reach target arterial pressures of 130–140/80–90 mmHg when transplanted with a kidney from a donor with a positive family history of hypertension than when transplanted with a kidney from a donor with a negative family history of hypertension (9).

Although evidence is more difficult to obtain under clinical conditions, these studies also show that in humans with primary hypertension arterial pressure can be normalized by a renal graft from normotensive donors (4). Furthermore, genetically determined variations in donor kidney function may be one cause of renal posttransplantation hypertension in patients (9). Given its clinical relevance in relation to the multiplicity of other factors involved in decision making, familial predisposition to hypertension in kidney donors may be of minor importance for the allocation of renal allografts to patients. Nevertheless, these data provide a strong rationale for further studies on renal mechanisms in genetic hypertension.

Perspectives on experimental renal transplantation in hypertension research

Sophisticated experimental animal breeding strategies and increasing possibilities of molecular genetic characterization of rat strains has led to a rising number of congenic and consomic rat lines available for hypertension research (3). In these inbred animals, defined genome fragments of normotensive origin have been exchanged with corresponding parts of the genome of a hypertensive inbred rat strain and vice versa. Microsurgical transplantation techniques involving congenic or consomic animals allow for so-called kidney-specific genome transfer (2). Thus it will be possible to characterize in greater detail what genes contribute to the susceptibility of the kidney to hypertensive renal damage and to further analyze the contribution of genetically determined renal and extrarenal mechanisms to the pathogenesis of genetic forms of hypertension.

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References


