The Kidney as a Determinant of Genetic Hypertension
Evidence From Renal Transplantation Studies
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Several lines of evidence suggest that the kidney plays an important role in the genesis of primary hypertension in humans and genetic hypertension in animals. Perhaps the most compelling evidence derives from clinical1–4 and experimental renal transplantation studies,5–36 which have been performed over the last 3 decades. In virtually all of these studies, the genetic background of the donor kidney had a major impact on long-term blood pressure in the recipients. More specifically, renal grafts from genetically hypertensive donors increased blood pressure in genetically normotensive recipients, whereas renal grafts from genetically normotensive donors lowered blood pressure in genetically hypertensive recipients. In many but not all of the studies, blood pressure traveled with the kidney in both directions. Although these data clearly show that the kidney is an important determinant of long-term blood pressure in normotension and primary or genetic hypertension, several major problems still remain unresolved. These problems relate mainly to the interpretation of the data and to the potential mechanisms by which the kidney sets the level of long-term blood pressure. In this brief review, we discuss the results and implications of clinical and experimental renal transplantation studies in primary hypertension in humans and genetic hypertension in animals that have been published to date.

Clinical Renal Transplantation Studies in Primary Hypertension
In the mid-1980s, 3 studies1,2,4 on renal transplant patients were published that supported a major role for the kidney in human essential hypertension. The classical study by Curtis et al1 demonstrated the sustained remission of essential hypertension caused more severe hypertensive hypertension in adults.5,6 and prevented the development of hypertension in young MHS.13 Furthermore, in all6,13 but the initial study,5 solitary kidney grafts from MHS donors caused sustained increases in blood pressure in genetically normotensive recipients. Thus, overall published evidence largely, although

Early Renal Transplantation Studies in Genetically Hypertensive Rats
Although renal transplantation studies in small rodents are technically demanding, they are usually straightforward by design and potential confounders, including variations in renal function or graft rejection, and can be easily controlled or completely avoided, respectively. In the literature, experimental renal transplantation studies in genetically hypertensive rats appeared in 2 waves: 1 peaking in the mid-1970s and the other still ongoing, starting in the early 1990s.

Early studies were performed in Milan hypertensive rats (MHS),5,6,13 Dahl salt-sensitive hypertensive rats10–12 (DS), and spontaneously hypertensive rats (SHR).26 These studies5,6,10–13,26 essentially showed that blood pressure in renal transplanted rats “was largely determined by the genotype of the donor kidney rather than by the genotype of the recipient.”12

In their experiments, Dahl et al studied 3 groups of rats with a single DS kidney, namely unilaterally nephrectomized DS, DS with a transplanted DS kidney, and Dahl salt-resistant rats (DR) with a transplanted DS kidney, as well as 3 corresponding groups of rats with a single DR kidney. On a diet containing 0.3% NaCl, all groups with a single DS kidney were hypertensive, whereas all groups with a single DR kidney were normotensive. Thus, blood pressure “traveled with the kidney” in these experiments. Dahl’s original findings were elegantly confirmed some 15 years later.28 In their early work, Dahl et al also reported that a solitary kidney graft from DR donors did not prevent hypertension in DS rats under high-salt diet (8.0% NaCl). This finding was also confirmed later28 and, in retrospect, may have been the first evidence from renal transplantation studies indicating that extrarenal factors also contribute significantly to genetic hypertension.

In Milan rats,5,6,13 a kidney graft from Milan normotensive rats normalized blood pressure in bilaterally nephrectomized adult MHS and prevented the development of hypertension in young MHS.13 Furthermore, in all6,13 but the initial study,5 solitary kidney grafts from MHS donors caused sustained increases in blood pressure in genetically normotensive recipients. Thus, overall published evidence largely, although
not exclusively, indicates that blood pressure travels with the kidney in Milan rats.

In SHR, the lack of an immunologically compatible normotensive control strain precludes direct renal cross-transplantations between hypertensive and normotensive animals. Fortunately, F1 hybrids bred from SHR and normotensive Wistar-Kyoto rats (WKY) do not reject grafts from their parental strains and may therefore serve as recipients in renal transplantation studies. In an initial study, Kawabe et al showed that solitary renal grafts from SHR donors increased and grafts from WKY donors decreased blood pressure in F1 hybrids. Despite this finding, the authors concluded that there was no evidence for an antihypertensive effect of a “normal” kidney. This conclusion was based on the observation that recipients of an F1 hybrid kidney had similar blood pressures as recipients of a WKY kidney. Thus, kidney grafts from WKY donors lowered blood pressure in recipients only when compared with nontransplanted unilaterally nephrectomized F1 hybrids with a fully innervated kidney but not when compared with F1 hybrids with a transplanted and therefore denervated F1 hybrid kidney. The effect of a transplanted WKY kidney on blood pressure in F1 hybrid recipients may therefore have reflected the well-known effect of renal denervation on blood pressure in genetically hypertensive animals rather than the effect of genetic programming of the kidney for normotension. Already clearly recognized in the first renal transplantation study in SHR hypertension research, the issue of whether a genetically normotensive kidney would have a blood pressure–lowering effect could only be solved when new rat strains, including genetically normotensive ones that allow for direct renal cross-transplantations with SHR, became available (see below).

The second generation of experimental renal transplantation studies in the field of hypertension began after a gap of ~10 years in 1989, when we were able to show that solitary kidney grafts from stroke-prone SHR (SHRSP) donors transmitted hypertension to F1 hybrid recipients that had been bred from SHRSP and WKY parents. Shortly thereafter, Heller et al demonstrated in a fifth hypertensive rat strain (after DS, MHS, SHR, and SHRSP), namely the Prague hypertensive rat (PHR), that solitary kidney grafts from genetically hypertensive donors transmitted hypertension to normotensive recipients. The availability of a genetically similar normotensive control strain also allowed Heller et al to directly test the effects of a genetically normotensive kidney graft on blood pressure in hypertensive recipients. In these experiments, the recipients’ blood pressure remained unchanged in unilaterally nephrectomized animals but dropped dramatically and immediately when the second native kidney was removed from the recipients several days after transplantation. The authors concluded from these results that the genetically hypertensive kidney most likely produces a hypertensinogenic substance, the nature of which unfortunately remains unclear. In an extension of their work, the Prague group provided some evidence that hypertension in genetically normotensive recipients of a PHR kidney may vanish within several months, whereas PHR recipients of a Prague normotensive rat kidney remained permanently normotensive.

In our studies in the SHRSP model of hypertension, we were concerned with yet another potential confounder, namely high renal perfusion pressure in the donors before removal of the grafts for transplantation. It is well known that the kidney is a target organ for hypertensive end-organ damage, and it appeared perfectly conceivable that hypertensive end-organ damage might have contributed to hypertension in recipients of an SHRSP kidney in our first study. Our finding that transplantation of the nonchipped kidney from 2-kidney-1-clip hypertensive rats caused hypertension in normotensive recipients was anything but reassuring with regard to the interpretation of the results that we had just obtained with transplanted SHRSP kidneys. In 2 different approaches to tackle this problem, we subjected SHRSP kidney donors to lifelong antihypertensive treatment and we performed renal transplantations with young prehypertensive donors. In both cases, the kidneys would carry the full genetic program for hypertension but never actually have been subjected to hypertensive perfusion pressure, excluding the possibility of hypertensive end-organ damage. In both studies, bilateral nephrectomized F1 hybrid recipients of an SHRSP kidney invariably developed hypertension, indicating that the genetic background for hypertension of the kidney was sufficient to cause hypertension in the recipients.

In the mid-1990s, it was clear from many studies that transplanted kidneys from 5 different genetically hypertensive rat strains would transmit hypertension to bilaterally nephrectomized genetically normotensive recipients. Only 1 study was negative, and another suggested a long-lasting (several months) but transient effect. The situation with respect to the ability of kidneys from genetically normotensive donors to lower blood pressure or to prevent hypertension from developing in young genetically hypertensive recipients has been less clear. Although solitary renal grafts from genetically normotensive donors consistently lowered blood pressure in MHS and PHR recipients as well as in DS recipients on a low-salt diet, it failed to do so in DS recipients on a high-salt diet. Our own work in SHRSP yielded inconsistent results. Transplantation of a WKY kidney to bilaterally nephrectomized F1 hybrids had no effect on blood pressure in 2 studies, whereas it decreased blood pressure compared with presurgical levels, unless nephrectomized F1 hybrid controls or recipients of an F1 hybrid kidney in other studies. This situation was, of course, highly unsatisfactory. Unfortunately, at that time, we did not have the means (ie, an appropriate genetically compatible normotensive control strain) to tackle this problem. Therefore, we focused our attention first on the mechanisms by which kidney grafts from hypertensive donors increased blood pressure in the recipients.

Renal Mechanisms of Hypertension

More than 3 decades after the first evidence that genetic hypertension can be transmitted with a kidney to normotensive recipients, the mechanisms underlying this phenomenon are still unclear. Possible mechanisms include: (1) the renin-angiotensin-aldosterone system, (2) renal sodium and volume handling, (3) sympathorenal interactions, and (4) (enhanced) production or inadequate excretion of a hitherto unknown substance.
hypertensinogenic substance. In several studies, we were able to demonstrate that the renin-angiotensin-aldosterone system is not stimulated in recipients of an SHRSP or SHR kidney. Interestingly, recipients of an SHRSP kidney had a lower 24-hour urinary aldosterone secretion, and recipients of an SHR kidney had lower plasma aldosterone concentrations than recipients of a kidney from normotensive donors. From these and other observations, we hypothesized that recipients of an SHRSP or SHR kidney, respectively, may have a primary defect in renal sodium handling. In fact, when we challenged our rats with a dietary sodium load, recipients of an SHRSP kidney showed a decreased renal capacity to excrete the load. The salt retention hypothesis was further supported when we found that hypertension in genetically normotensive recipients of an SHRSP kidney was associated with renal sodium retention that began when the contralateral native kidney was removed (ie, 7 days after transplantation).

However, if sodium retention was a causal factor for the development of hypertension in recipients of an SHRSP kidney, it should: (1) precede hypertension, (2) still be demonstrable when intestinal sodium loss is appropriately accounted for, and (3) give rise to some kind of measurable volume expansion. When radiotelemetric blood pressure recordings became available to us, it soon became clear that renal post-transplantation hypertension in recipients of an SHR kidney started to develop much earlier than thought previously (ie, within the very first days after transplantation and well before the removal of the second native kidney). A recent reinvestigation of the issue revealed that overall sodium balances and plasma volumes were similar in recipients of an SHR kidney and in recipients of an F1 hybrid kidney despite a significantly higher blood pressure in the former group.

Sodium may affect blood pressure by causing volume expansion or by increasing vascular reactivity. Therefore, we also investigated the contractile properties of recipient third-order mesenteric artery branches and of distal interlobar arteries from kidney grafts using a small-vessel wire myograph. There was no evidence for altered vasoconstrictory or vasodilatory properties in recipients of an SHR kidney versus recipients of an F1 hybrid kidney.

**Interactions Between the Sympathetic Nervous System and the Kidney**

The sympathetic nervous system interacts with the kidney at various levels to achieve normal control of blood pressure. Similar interactions may be involved in arterial hypertension. Although kidney grafts are necessarily completely denervated at the time of transplantation, reinnervation may occur. Furthermore, substances produced or retained by the kidney graft may affect the sympathetic nervous system of the recipients.

Tissue noradrenaline content in renal grafts dropped to \( \approx 3\% \) of control values and remained this low until \( \geq 9 \) months after transplantation. Thus, there was virtually no reinnervation within the time of interest in our studies. We also did not find any evidence for differences in the activity of the sympathetic nervous system between recipients of solitary kidney grafts from normotensive and hypertensive donors. In particular, we found similar adrenal tyrosine hydroxylase mRNA contents as well as similar blood pressure and directly recorded sympathetic nerve activity responses to central \( \alpha_2 \)-adrenergic stimulation with guanabenz.

Our failure to demonstrate increased sympathetic activity in F1 hybrids with a transplanted SHR kidney compared with F1 hybrids with a transplanted F1 hybrid kidney does not mean that the sympathetic nervous system does not contribute to SHR hypertension. In fact, we were able to directly demonstrate this contribution in our renal transplantation experiments. Thus, SHR recipients of an SHR kidney graft from neonatally sympathectomized donors had an \( \approx 20 \) mm Hg lower mean arterial pressure than SHR recipients of an SHR kidney graft from hydralazine-treated control donors. Furthermore, SHR kidney grafts increased mean arterial pressure by only \( \approx 20 \) mm Hg in neonatally sympathectomized F1 hybrids compared with \( \approx 35 \) mm Hg in untreated F1 hybrids. Together, these data indicate that the sympathetic nervous system contributes to hypertension in SHR via its actions on the kidney and nonrenal tissues. The kidney-mediated long-term effects on blood pressure of the sympathetic nervous system can be transmitted with the kidney to renal graft recipients. This situation is reminiscent of the long-term effects on blood pressure of transient angiotensin I→converting enzyme (ACE) inhibitor treatment, which have also been reported to be transmittable with the kidney in a setting of renal transplantation.

After it had been reported in the mid-1980s that transient ACE inhibitor treatment in young SHR caused a persistent blood pressure decrease, this effect was subsequently shown to be oblviated by a kidney graft from untreated SHR donors. More recently, Smallegange et al confirmed and extended these observations by showing that arterial pressure in untreated SHR recipients was persistently lowered after transplantation of a kidney from SHR donors that had been treated previously with an ACE inhibitor (Figure 1). Together, these data show that various nongenetic factors, including the sympathetic nervous system and certain antihypertensive drugs, may act transiently on the kidney, thereby persistently changing the renal set point for arterial pressure. The mechanisms underlying this phenomenon are currently unclear. One possibility is that these factors cause persistent changes in renal resistance artery function. However, we found no evidence for an influence of neonatal sympathectomy on proximal renal resistance artery function in SHR that would persist after renal transplantation, and that might explain the differences in blood pressure between F1 hybrid recipients of an SHR kidney from neonatally sympathectomized versus hydralazine-treated donors.

As outlined above, the results of experimental renal transplantation studies show that the genetic background of the kidney graft is a major determinant of blood pressure in the recipients, sometimes clearly overriding other factors. They also show that nongenetic factors may persistently change the renal set point for arterial pressure, and they finally show that nonrenal mechanisms contribute importantly to genetic hypertension. These different factors are by no means mutually

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The data show that the nephrectomized SHR with transplanted CSHR kidney) or normotensive BN either only within the kidney (bilaterally or outside the kidney) was sufficient to lower blood pressure compared with autotransplanted SHR controls that did not have the DNA segment from the BN rat. These data support the idea that the kidney plays a major role in SHR hypertension by showing that the replacement of the native kidneys by a CSHR kidney graft persistently lowered blood pressure in SHR. In addition, the data provide evidence for a major contribution of nonrenal mechanisms to SHR hypertension by showing that the transferred DNA segment exerted the same blood pressure–lowering effect regardless of whether it was present only in renal or only in nonrenal tissues.

Given the complexity created by multiple blood pressure–regulating systems and their mutual interactions, the above-mentioned results may not really come as a great surprise. In fact, the pioneering work by Dahl et al already showed that a genetically “normotensive” kidney was not sufficient to prevent hypertension in DS rats under high-salt diet, and many other studies, including some of our own, found blood pressure to travel with the kidney in one (usually upwards) but not the other direction. What may be more remarkable than the likely contribution of nonrenal factors to genetic hypertension is the fact that none of the renal transplantation studies in the field of hypertension published to date failed to clearly demonstrate a major role of the kidney in genetic hypertension: not as the sole factor that may be exclusively responsible for the disease but certainly as the single factor for which the major contribution to genetic hypertension can be demonstrated most robustly.

Another recent study\(^6\) used congenic WKY (ConWKY) harboring a segment of chromosome 1 from SHR. Systolic blood pressure was \(\approx 20\) mm Hg higher in ConWKY than in the progenitor WKY strain. The increment in blood pressure in ConWKY versus WKY was largely transmitted with a chromosome 1 is mediated through the kidney. The 2 studies using chromosome 1 congenic rats\(^8,9\) are at variance with each other with respect to the kidney-mediated blood pressure effects of loci on chromosome 1. Whereas one study\(^8\) found that the kidney-specific transfer of a DNA segment from SHR had no effect on blood pressure in the recipients, the other study\(^9\) found an increase in blood pressure. The reasons for this discrepancy are unclear. The DNA segments transferred in the 2 studies\(^8,9\) were overlapping but not identical. They contain many genes, including the \(S\alpha\) gene and the closely linked genes encoding the \(\beta\) and \(\gamma\) units of the epithelial sodium channel that were associated with blood pressure in several studies.\(^38,39\)

Recently, our group used a combination of renal transplantation with congenic strain technology to overcome the problem of graft rejection when a kidney graft from normotensive donors is transplanted into SHR recipients. We had evidence from a previous renal transplantation study in SHR and inbred Biobreeding/Ottawa Karlsburg rats (BB/OK) showing that hypertension in SHR may depend on the presence of a kidney with the genetic background for hypertension.\(^29\) However, in this study,\(^29\) imminent graft rejection caused some concern. To overcome this problem, a congenic

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**Figure 1.** Persistent lowering of mean arterial pressure (MAP) in untreated SHR recipients of a kidney graft from SHR donors that had been treated previously with an ACE inhibitor (reprinted with permission from Smallegange et al, *Hypertension* 2003). UNX indicates unilateral nephrectomy.

**Studies in New Congenic Strains**

Harrap et al\(^{22}\) may have been the first to consider a specific segment of the genome (the Y chromosome) rather than the entire genetic background of grafts and recipients when they designed a renal transplantation study between male and female SHR \(>10\) years ago. They were aware of the reports showing that hypertension in SHR can be transmitted with the kidney to genetically normotensive recipients and, they reasoned that the difference in blood pressure between male and female SHR may be attributable to inherent differences between the kidneys of the 2 sexes. However, the results were negative; neither did a male kidney graft raise blood pressure in female SHR recipients, nor did a female kidney graft lower blood pressure in male recipients.\(^{22}\)

Later attempts to narrow down a specific segment of the genome that may be responsible for the phenomenon that blood pressure often follows the kidney in renal transplantation studies were more successful.\(^{8,9}\) One study\(^8\) used a congenic SHR (CSHR) strain that harbors a 22-cM segment of chromosome 1 from the normotensive Brown-Norway rat (BN). Systolic blood pressure was \(\approx 20\) mm Hg lower in CSHR than in the progenitor SHR strain. By performing renal cross-transplantations between SHR and CSHR, the authors generated animals that were identical with respect to their genetic SHR background but in which a specific segment of the genome was exchanged by the homologous segment from normotensive BN either only within the kidney (bilaterally nephrectomized SHR with transplanted CSHR kidney) or only within all nonrenal tissues (bilaterally nephrectomized CSHR with transplanted SHR kidney). The data show that the presence of the transferred DNA segment (either inside or outside the kidney) was sufficient to lower blood pressure compared with autotransplanted SHR controls that did not have the DNA segment from the BN rat. These data support the idea that the kidney plays a major role in SHR hypertension by showing that the replacement of the native kidneys by a CSHR kidney graft persistently lowered blood pressure in SHR. In addition, the data provide evidence for a major contribution of nonrenal mechanisms to SHR hypertension by showing that the transferred DNA segment exerted the same blood pressure–lowering effect regardless of whether it was present only in renal or only in nonrenal tissues.

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**Table 1.** Persistent lowering of mean arterial pressure (MAP) in untreated SHR recipients of a kidney graft from SHR donors that had been treated previously with an ACE inhibitor (reprinted with permission from Smallegange et al, *Hypertension* 2003). UNX indicates unilateral nephrectomy.
Figure 2. Persistent lowering of mean arterial pressure (MAP) in bilaterally nephrectomized SHR recipients of kidney from non-nephromensive BB.1K donors (reprinted with permission from Grisk et al, J Hypertens 2002). TX indicates transplantation; NX, nephrectomy.

The strain (BB.1K) was developed from BB/OK progenitors that harbors a 2-cM segment of SHR chromosome 20 containing the rat major histocompatibility loci. Naive BB.1K is perfectly normotensive. Transplantation of a BB.1K kidney graft into bilaterally nephrectomized SHR recipients resulted in rapid and persistent blood pressure normalization with mean arterial pressures of ~100 mm Hg (Figure 2). The reduction in blood pressure was associated with a significant decrease in the left ventricular weight-to-body weight ratio. Together, these data indicate that hypertension in SHR is not maintained when the native kidneys are removed and replaced by a well-functioning kidney graft that does not carry the genetic background for hypertension.

Most recently, renal cross-transplantation has been combined with gene knockout technology in mice. In this study, angiotensin II type 1A receptor (AT_{1A})–deficient mice had lower blood pressures than wild-type controls. Rats that expressed the AT_{1A} receptor only within the kidney (AT_{1A}-deficient recipients of a wild-type kidney) or only within nonrenal tissues (wild-type recipients of an AT_{1A}-deficient kidney) had similar blood pressures, which were lower than that of autotransplanted wild-type controls but higher than that of autotransplanted AT_{1A}-deficient mice. These data indicate that AT_{1A} receptors in the kidney and in nonrenal tissues contribute similarly to normal blood pressure.

Summary and Perspectives

Over the last 3 decades, a few clinical and many experimental renal transplantation studies have been performed in hypertension research. The results of virtually all of these studies support the notion that the kidney is a major determinant of long-term blood pressure and plays a major role in the pathogenesis of primary hypertension in humans and genetic hypertension in animals. Experimental renal transplantation studies in rats have also provided evidence for important contributions of nonrenal mechanisms, such as the sympathetic nervous system, to genetic hypertension. The specific mechanisms by which kidney grafts from genetically hypertensive donors elicit hypertension in genetically normotensive recipients and vice versa are currently unknown. Novel integrated molecular genetic approaches, such as the combination of transcriptional profiling with linkage analysis or mapping of quantitative trait loci, will help to identify genetic renal mechanisms of hypertension. Renal transplantation experiments using congenic or knockout animals will provide evidence for the impact of renal genetic variations on chronic arterial pressure. Addition of established and innovative sophisticated physiological techniques to investigate renal function, body fluid and electrolyte balance, and neurohormonal systems as well as extrarenal hemodynamics with sufficient precision and time resolution is necessary to better understand how changes in renal function are transmitted into arterial hypertension.

References


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