Nephron Number, Renal Function, and Arterial Pressure in Aged GDNF Heterozygous Mice

Luise A. Cullen-McEwen, Michelle M. Kett, John Dowling, Warwick P. Anderson, John F. Bertram

Abstract—The loss of one allele for glial cell line–derived neurotrophic factor (GDNF) results in \( \sim 30\% \) fewer but normal sized glomeruli in young mice. Low nephron number, inherited or acquired, has been linked to increased risk of development of hypertension and renal failure. This study examines whether GDNF heterozygous mice, with an inherent reduction in nephron number, demonstrate a deterioration in renal structure and function and rise in arterial pressure in later life. Fourteen-month-old male GDNF heterozygous (n=7) and wild-type (n=6) mice were anesthetized and prepared for measurement of mean arterial pressure, glomerular filtration rate (GFR), and renal blood flow. After measurement of renal function, kidneys were fixed for stereological determination of total glomerular number and mean glomerular volume. Mean arterial pressure was, on average, 18 mm Hg higher in GDNF heterozygous (98±4 mm Hg) than wild-type mice (80±2 mm Hg; \( P<0.01 \)). However, GFR (0.656±0.054 versus 0.688±0.076 mL/min per g kidney wt) and renal blood flow (5.29±0.42 versus 4.70±0.34 mL/min per g kidney wt) were not different between groups. Fourteen-month-old GDNF heterozygous mice had \( \sim 30\% \) fewer glomeruli than wild-type mice (9206±934 versus 13440±1275; \( P<0.01 \)) and significantly larger glomeruli (4.51±0.39 versus 3.72±0.63×10\(^{-2}\) mm\(^3\); \( P<0.01 \)). Thus, aged GDNF heterozygous mice maintained a normal GFR and renal blood flow despite reduced nephron numbers. The elevated arterial pressure, glomerular hypertrophy, and hyperfiltration demonstrated in the GDNF heterozygous mice at this age may indicate a compensatory mechanism whereby GFR is maintained in the presence of a reduced nephron endowment. (Hypertension. 2003;41:335-340.)

Key Words: mice ■ hypertension, genetic ■ kidney ■ blood flow ■ arterial pressure

It has been hypothesized that low nephron numbers in the kidney may increase the risk of development of cardiovascular diseases such as hypertension and chronic renal failure and reduce the long-term success of renal allografts.\(^1\)\(^-\)\(^4\) Thus, factors that affect nephrogenesis in the fetus may not only be critical in kidney development but also affect subsequent adult kidney function and underlie much subsequent renal pathology and abnormal physiology.

Glial cell line–derived neurotrophic factor (GDNF)\(^5\)\(^-\)\(^7\) has been shown to play a key role in kidney development through actions at the RET and GFR\(\alpha1\) receptor and coreceptor.\(^8\)\(^,\)\(^9\) Specifically, GDNF has been demonstrated to initiate budding of the ureteric duct from the Wolffian duct, branching of the ureteric epithelium within the metanephric mesenchyme, and the formation of new nephrons at the branch tips.\(^5\)\(^-\)\(^7\) Increasing the levels of exogenous GDNF in metanephric culture medium leads to increases in both the number of ureteric branches and number of developing nephrons.\(^7\) In the late 1990s, knockout studies demonstrated that homozygous null mutants for GDNF,\(^10\)\(^-\)\(^13\) as well as RET\(^14\) and GFR\(\alpha1\),\(^15\)\(^,\)\(^16\) showed bilateral renal agenesis and died shortly after birth. In contrast, GDNF, RET, and GFR\(\alpha1\) heterozygous mice were both fertile and viable. Whereas the RET and GFR\(\alpha1\) heterozygotes demonstrated a normal renal phenotype, the GDNF heterozygotes showed an array of renal phenotypes, ranging from two smaller kidneys, many with abnormal shapes and cortical cysts, to unilateral renal agenesis.\(^10\)\(^-\)\(^13\)

These results indicated that GDNF gene dosage influenced kidney development, with the loss of one allele being sufficient to cause a significant renal phenotype. Recently we found that the kidneys of these GDNF heterozygous mice at 30 days of age were \( \sim 25\% \) smaller than their wild-type littermates despite similar body weights.\(^17\) Furthermore, stereologic estimates of nephron number identified a 30% decrease in nephron endowment in young heterozygous GDNF mice compared with wild-type mice. The GDNF heterozygous mouse thus provides a genetic model with which to test the hypothesis that an inherent reduction in nephron number contributes to the development of cardiovascular and renal disease that is uncomplicated by changes in birth and body weight. In the majority of cases in humans,
cardiovascular and renal disease does not become apparent until later in life. Thus this study examines whether GDNF heterozygous mice with a 30% reduction in nephron endowment go on to demonstrate a deterioration in renal function, glomerular hypertrophy, and/or increases in arterial pressure later in life.

Methods

All experiments were approved in advance by Monash University Departments of Physiology and Anatomy and Cell Biology Animal Ethics Committees and were conducted in accordance with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes.

Our GDNF mouse colony was initially established with founders from the laboratory of Dr Heiner Westphal (Laboratory of Mammalian Genes and Development, National Institutes of Health, Bethesda, Md).10,11 Male GDNF heterozygous mice (129Sv-C57BL/6 hybrid; 6th generation C57BL/6 back-cross) were mated with female C57BL/6 mice. After weaning, tail tissue was obtained from all mice for genotyping by polymerase chain reaction,10,11,17 and the mice classified Genes and Development, National Institutes of Health, Bethesda, Md).10,11 Male GDNF heterozygous mice (129Sv-C57BL/6 hybrid; 6th generation C57BL/6 back-cross) were mated with female C57BL/6 mice. After weaning, tail tissue was obtained from all mice for genotyping by polymerase chain reaction,10,11,17 and the mice were coded such that the following experiments were carried out in a blinded fashion.

Blood Pressure and Renal Function

At 14 months of age, male GDNF wild-type (14.0±0.3 months; n=7) and heterozygous (14.1±0.2 months; n=6) mice were anesthetized (Inactin, 100 mg/kg IP; Sigma Chemical Co; and ketamine, 10 mg/kg IP; Parnell Laboratories) and placed on a heating table to maintain body temperature at 37°C. The trachea was catheterized (PE-90), and a stream of O2 was blown onto the end of the tube to maintain a stable arterial pressure throughout the experiment. The left femoral artery was catheterized (pulled SV-50) for measurement of blood pressure and heart rate and to obtain a terminal arterial blood sample, and the left femoral vein (pulled SV-50) was catheterized for infusion of maintenance fluids (6% BSA, 2.5 μL/min during surgery). After surgery, the infusion was changed to a 1% BSA solution containing 14 C-PAH (1.7 μCi/mL) and 3 H-inulin (5.58 μCi/mL) and 14 C-PAH (1.7 μCi/mL) for estimation of glomerular filtration rate (GFR) and effective renal plasma flow by renal clearance methods, and the mice were allowed 1 hour to equilibrate. The equilibration period was followed by two 20-minute urine collection periods, after which an arterial blood sample (100 μL) was taken. Urinary protein concentrations were measured by means of the Bradford method.18 Sodium and potassium concentrations were analyzed with a Technicon autoanalyzer flame photometer IV.

At the completion of the experiment, kidneys were rapidly excised, weighed, and immersion-fixed in 2% paraformaldehyde and 2% glutaraldehyde in 0.1 mol/L phosphate buffer. The left kidneys were then processed for embedding in glycolmethacrylate for stereologic estimation of total nephron number and mean glomerular volume. Right kidneys were processed and embedded in paraffin, exhaustively sectioned at 20 μm, and every 10th and 11th section was collected and stained with periodic acid Schiff’s reagent, and Masson’s trichrome stain for assessment of renal pathology.

Estimating Kidney Volume

Kidney volume was estimated by means of the Cavalieri principle.19,20 Briefly, whole kidneys embedded in glycolmethacrylate were exhaustively sectioned at 20 μm, and every 10th and 11th section was collected and stained with periodic acid Schiff’s reagent. The “10th” section of each pair was then placed on a microfiche reader (magnification ×24.25), and a stereologic test grid (2×2 cm) was placed on the microfiche screen. Kidney volume (Vkid) was estimated using the formula:

\[ V_{kid} = \sum P \times a(p) \times T \times 1/f \]

where \( P \) is the total number of points counted, \( a(p) \) is the area associated with each grid point, \( T \) is section thickness, and \( 1/f \) is the inverse of the section sampling fraction.

Estimating Nephron Number

The above section pairs were used to estimate nephron number, using the physical disector/fractionator combination.20–22 Briefly, the section pairs were projected side by side, with two microscopes modified for projection. One microscope was fitted with a motorized stage and the other was fitted with a rotating stage to enable section alignment. A grid was placed over each field of view, and points falling on kidney tissue (Nglom), glomeruli (Nglomeruli), and renal corpuscles (Ncorpus) were counted. Glomeruli sampled by an unbiased counting frame in the field of view of the 10th section that were not present in the 11th section were counted. Those sampled in the 11th section that were not present in the 10th section were counted to double the efficiency of the technique. This process was repeated for each complete pair of sections. Total nephron number (Nglomeruli) was then estimated using the following equation:

\[ N_{glomeruli} = 10 \times P_s / P_f \times 1 / 2f \times Q^- \]

where 10 was the reciprocal of the section sampling fraction, \( P_s \) the number of points overlaying all kidney sections, \( P_f \) the number of points overlaying complete kidney sections, \( 1/2f \) the fraction of the total section area used to count glomeruli, and \( Q^- \) the actual number of glomeruli counted.

Glomerular Volume

Mean glomerular volume (Vglom) was estimated by using the following formula:

\[ V_{glomeruli} = \frac{[V_{glomeruli}, V_{total}]}{[N_{glomeruli}, V_{total}]} \]

where \( V_{glomeruli}, V_{total} \) and \( V_{glomeruli}, V_{total} \) are equivalent to \( F_{glomeruli}, F_{total} \).

The total volume of all glomeruli (Vglomerular) in the kidney was estimated by using the following formula:

\[ V_{glomerular} = V_{glomeruli} \times N_{glomeruli} \]

These formulas were then adjusted for estimation of mean renal corpuscle volume (Vcorpus) and total volume of all renal corpuscles in the kidney (Vcorpus).

Statistics

Differences between heterozygous and wild-type mice were tested with an unpaired Student t test. Values are presented as mean±SEM except for stereological data, which are presented as mean±SD.

Results

At 14 months of age, there were no significant differences in GFR, renal blood flow, renal vascular resistance, filtration fraction, fractional sodium and potassium excretions, or urinary protein concentration between GDNF heterozygous and wild-type mice (Table 1). In contrast, anesthetized mean arterial pressures were 18 mm Hg higher in GDNF heterozygotes than their wild-type littermates (P<0.001; Table 1). There were no differences in body or kidney weights between the two groups (Table 1).

Stereology

Consistent with kidney weights, stereologic estimates of kidney volume were not significantly different between GDNF heterozygous mice and wild-type littermates (Table 2). Total nephron number estimates confirmed the results obtained at 30 days of age, with aged male GDNF heterozygous mice also containing ≈30% fewer nephrons than their wild-type littermates (P<0.01). At 14 months, however, the glomeruli of GDNF heterozygous kidneys were 20% larger (P<0.01) and mean renal corpuscle volume 30% larger than
Glomerular volume, /H11003
Stereological Parameter Wild-Type and Heterozygous 14-Month-Old Mice

of necrosis or apoptosis. Despite significant hypertrophy, the (Figure). There was no evidence of degeneration within the much greater and more widespread than in wild types tubular vacuolation; however, the extent of vacuolation was mild inflammation around the heterozygotes, however, were indistinguishable from wild-type littermates in terms of body weight but had reduced renal mass. Recently, our group published a detailed stereological analysis of glomerular number and volumes in these GDNF heterozygous mice, studying the mice at 30 days of age when kidney development is complete. We found that glomerular number was 30% lower than wild-type littermates, although glomerular volumes were similar at this age.17

The GDNF heterozygous mouse thus provides a unique animal model with which to examine whether reduced glomerular endowment at birth is a predictor of subsequent development of cardiovascular disease such as essential hypertension later in life. GDNF heterozygous and wild-type mice start to die of natural causes at around 16 months and therefore we chose to study them at 14 months, making the assumption that this was equivalent to late middle age in humans, when the incidence of cardiovascular diseases such as essential hypertension rises markedly in the population. It has been hypothesized that reductions in glomerular number leads to hypertrophy of the remaining glomeruli with time. This has been well documented in the commonly used 5/6 nephrectomy model. The present study appears to indicate that such hypertrophy also occurs when glomerular numbers are reduced genetically. We previously reported that young GDNF heterozygous mice (30 days old) showed reduced glomerular numbers with no change in mean glomerular volume and thus demonstrated, overall, a reduced total glomerular volume (product of glomerular number and volume). In the current study, we found that by 14 months of age, glomeruli of GDNF heterozygotes were significantly hypertrophied such that the total glomerular volume was no longer different between wild-type and heterozygous littermates. Whole-kidney GFR, renal blood flow, and fractional excretions were also not different between wild-type and GDNF heterozygous littermates. Although micropuncture analysis was not performed in this study, an index of average single nephron function can be calculated by dividing whole-kidney GFR by the number of glomeruli. With 30% fewer nephrons and similar GFR, GDNF heterozygous mice appear to have marked hyperfiltration with 30% greater calculated single nephron GFR values compared with wild-type mice (17.7±1.3 and 13.5±1.2, respectively; P<0.05). Such glo-

Discussion

A low renal nephron number ("reduced nephron endowment") has been linked with the development of hypertension, glomerulosclerosis, renal failure, and the long-term failure of renal allografts. There are, however, few available animal models with a congenital nephron deficit uncomplicated by changes in birth and adult body weight with which to examine this link. In 1996, three independent research groups generated mice with a homozygous null mutation for GDNF.10,12,13 The homozygous null mutants died within the first 24 hours of postnatal life as the result of bilateral renal agenesis. The heterozygotes, however, were indistinguishable from wild-type littermates in terms of body weight but had reduced renal mass. Recently, our group published a detailed stereological analysis of glomerular number and volumes in these GDNF heterozygous mice, studying the mice at 30 days of age when kidney development is complete.17 We found that glomerular number was 30% lower than wild-type littermates, although glomerular volumes were similar at this age.17

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### TABLE 1. Characteristics of 14-Month-Old Wild-Type and GDNF Heterozygous Mice

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Wild-Type</th>
<th>GDNF Heterozygous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, g</td>
<td>47±2</td>
<td>46±1</td>
</tr>
<tr>
<td>Left kidney weight, g</td>
<td>0.277±0.023</td>
<td>0.259±0.031</td>
</tr>
<tr>
<td>Right kidney weight, g</td>
<td>0.283±0.026</td>
<td>0.245±0.012</td>
</tr>
<tr>
<td>Total kidney weight, g</td>
<td>0.560±0.048</td>
<td>0.503±0.033</td>
</tr>
<tr>
<td>Glomerular number</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney volume, mm³</td>
<td>276.5±32.1</td>
<td>247.8±54.5</td>
</tr>
<tr>
<td>Glomerular volume, ×10⁻³mm³</td>
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</tr>
<tr>
<td>Total glomerular volume, mm³</td>
<td>4.99±0.87</td>
<td>4.15±0.55</td>
</tr>
<tr>
<td>Corpuscle volume, ×10⁻³mm³</td>
<td>5.69±0.44</td>
<td>7.38±0.59</td>
</tr>
<tr>
<td>Total corpuscle volume, mm³</td>
<td>7.67±1.13</td>
<td>6.81±1.10</td>
</tr>
</tbody>
</table>

Values are mean±SD. Wild type n=7; GDNF heterozygous n=6. *P<0.01.

### TABLE 2. Stereological Estimates for the Left Kidneys of Wild-Type and Heterozygous 14-Month-Old Mice

<table>
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wild-type kidneys (P<0.01; Table 2). Total glomerular and renal corpuscle volumes (product of glomerular number and glomerular/corpuscle volume) were not different between wild-type and GDNF heterozygous kidneys.

Renal Histology and Pathology

Kiddes of 14-month-old GDNF heterozygous and wild-type mice both showed evidence of tubulointerstitial pathology. Most wild-type kidneys analyzed showed areas of focal tubular vacuolation (Figure) and mild inflammation around the renal pelvis. GDNF heterozygous kidneys also showed tubular vacuolation; however, the extent of vacuolation was much greater and more widespread than in wild types (Figure). There was no evidence of degeneration within the vacuolated cells as they displayed viable nuclei and no signs of necrosis or apoptosis. Despite significant hypertrophy, the glomeruli of GDNF heterozygous kidneys showed no evi-

dence of sclerosis or hypercellularity (Figure). In addition, of the GDNF heterozygous kidneys analyzed, one showed areas of focal interstitial inflammation and one contained a cortical cyst.
merular hypertrophy and hyperfiltration is often a predictor of glomerular damage and progression to glomerular sclerosis. However, GDNF heterozygous mice showed no evidence of glomerular sclerosis or increased proteinuria at 14 months of age. GDNF heterozygous mice did demonstrate greater proximal tubule vacuolation at 14 months of age compared with wild-type mice. The significance of these changes on tubular reabsorption in the GDNF mice are as yet unclear; however, the fractional excretion of sodium and potassium were not different between wild-type and GDNF heterozygous littermates.

Finally, we found that these old GDNF heterozygous mice had mean arterial pressures that were 18 mm Hg higher than their wild-type littermates. At this time, we are not able to say when arterial pressure became elevated. Gerlai et al., however, reported that the mean arterial pressure of 4- to 7-month-old GDNF heterozygous and wild-type mice were not significantly different, suggesting the elevation in pressure observed in the present study occurs subsequent to this. Interestingly, this group also showed plasma creatinine levels of the GDNF heterozygous mice to be 10 times higher than wild-type mice, suggesting that GFR tended to be decreased in younger normotensive GDNF heterozygous mice. These findings are compatible with Brenner’s hypothesis that a reduced filtration surface area leads to the development of glomerular hypertrophy and hypertension in order to maintain adequate renal function. These findings suggest that the GDNF heterozygous mice may prove to be a useful model of essential hypertension. While anesthesia with Inactin and ketamine has been found to have only mild effects on arterial pressure, conscious, sequential blood pressure recordings and renal functions at different ages during the lifespan of the GDNF mice are required to document the time course and accurately determine the degree of the elevation in arterial pressure and changes in glomerular structure and renal function.

A number of experimental models of reduced nephron number have been previously used to study the association between nephron number and blood pressure, each with significant limitations. Rats born to pregnant dams fed a low protein diet do show reduced nephron number; however, they have other major phenotype differences from control mice such as reduced body weight, which confounds simple interpretation of the results. With 5/6 nephrectomy, the extent of nephron reduction is much more severe than would be expected in the natural genetic variation in humans. Mice overexpressing human insulin-like growth factor also have reduced nephron endowment with glomerular numbers 20% lower than control mice, but at this time there have been no reports on renal function or blood pressure of these mice.

GDNF mice have the advantage that their body weights are similar to their wild-type control mice from birth; indeed the control mice have the added advantage of being littermates, and the gene manipulated has a specific role in nephrogenesis itself. GDNF has been shown to be a potent survival factor for a variety of neuronal populations in vitro and in vivo, and some of these populations are reduced in the GDNF null mutant mice. However, apart from a reduction in the number of Aβ-caliber sensory nerve endings in the adult but not neonatal whisker follicle and an impairment in learning the position of a hidden platform in a water maze task, the GDNF heterozygous mouse appears to have normally functioning dopaminergic, noradrenergic, and motor systems. Recently, Shen et al. reported hypoganglionosis of the gastrointestinal tract of GDNF heterozygous mice with up to 1 in 5 GDNF heterozygous mice dying before weaning because of complications resulting from enteric aganglionosis. It is important to note that GDNF heterozygous mice with hypoganglionosis were asymptomatic and thus, given the similar body weights and fecal pellets of GDNF heterozygous and wild-type littermates in the current study, it appears unlikely that enteric hypoganglionosis contributed to the
higher blood pressure seen in these 14-month-old GDNF heterozygous mice. Of course, one cannot exclude the possibility that undetected phenotypes might also affect the cardiovascular outcomes in these mice.

Interestingly, an acquired nephron deficit after surgical reduction of renal mass does not always lead to hypertension, even when the reduction is greater than the 30% congenital loss demonstrated in GDNF heterozygous mice. A 50% reduction in glomerular number after unilateral nephrectomy in rats does not lead to the development of hypertension unless the nephrectomy is performed just after birth.32,33 In humans, adult unilateral nephrectomy does not lead to increased prevalence of hypertension in kidney donors unless these donors have underlying conditions such as obesity or diabetes.34,35 However, there does appear to be an increased risk of hypertension for patients who had a kidney removed as children because of Wilms tumor.36,37 Even more dramatic losses in renal mass such as those seen with surgical five-sixths nephrectomy does not always lead to hypertension in rats unless generated by unilateral nephrectomy plus infarction of two thirds of the other kidney.38 Of course, with these surgical models of renal and glomerular deficit, there is an acute and quite dramatic physiological reaction to the loss of renal mass involving the renal sympathetic nervous system and various hormonal systems leading to immediate (minutes) doubling of sodium and potassium excretion and followed by (hours-days) marked elevations in GFR, renal blood flow, and cardiac output, falls in renal vascular resistance, and compensatory growth of the remaining renal tissue in the following days to weeks.38–43 Such dramatic changes cannot be compared with the situation of inherent nephron deficit in which, one could argue, there is no acute physiological reaction but rather a slow adaptive response to the growing needs of the animal.

In summary, mice heterozygous for the GDNF gene that have 30% fewer nephrons than wild type show elevated arterial pressure, normal GFR, and thus hyperfiltration in old age. Unlike the situation at 1 month, glomeruli of 14-month-old GDNF heterozygous mice are hypertrophied; however, this occurs without evidence of glomerular pathology. Thus, the results found in this low nephron-number mouse, uncomplicated by changes in body weight, are in accord with the hypothesis of Brenner et al2 that a reduction in nephron number from birth leads to the development of hypertension and hyperfiltration.

Perspectives

Several animal models exist to examine the link between acquired reductions in nephron number and the subsequent development of cardiovascular and renal diseases; however, there are few animal models of congenital nephron deficit. Our current results suggest that the GDNF heterozygous mouse, with an inherent 30% reduction in nephron number, may provide a useful animal model to study the role of nephron endowment in the pathogenesis of essential hypertension.

Acknowledgments

This work was supported by the Australian Research Council. Luise Cullen-McEwen was funded by a Biomedical Research Scholarship from the Australian Kidney Foundation. Michelle Kett was funded by a National Health and Medical Research Council Project Grant (124404). The authors would like to acknowledge the assistance of Katrina Worthy.

References


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Hypertension. 2003;41:335-340; originally published online January 13, 2003;
doi: 10.1161/01.HYP.0000050961.70182.56
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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