Loss of a kidney during fetal life: long-term consequences and lessons learned

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Lankadeva YR, Singh RR, Tare M, Moritz KM, Denton KM. Loss of a kidney during fetal life: long-term consequences and lessons learned. Am J Physiol Renal Physiol 306: F791–F800, 2014. First published February 5, 2014; doi:10.1152/ajprenal.00666.2013.—Epidemiological studies reveal that children born with a solitary functioning kidney (SFK) have a greater predisposition to develop renal insufficiency and hypertension in early adulthood. A congenital SFK is present in patients with unilateral renal agenesis or unilateral multicystic kidney dysplasia, leading to both structural and functional adaptations in the remaining kidney, which act to mitigate the reductions in glomerular filtration rate and sodium excretion that would otherwise ensue. To understand the mechanisms underlying the early development of renal insufficiency in children born with a SFK, we established a model of fetal uninephrectomy (uni-x) in sheep, a species that similar to humans complete nephrogenesis before birth. This model results in a 30% reduction in nephron number rather than 50%, due to compensatory nephrogenesis in the remaining kidney. Similar to children with a congenital SFK, uni-x sheep demonstrate a progressive increase in arterial pressure and a loss of renal function with aging. This review summarizes the compensatory changes in renal hemodynamics and tubular sodium handling that drive impairments in renal function and highlights the existence of sex differences in the functional adaptations following the loss of a kidney during fetal life.

hypertension; renal compensatory growth tubular sodium reabsorption; renin angiotensin system; vasopressin; nitric oxide; aging

A Solitary Functioning Kidney: Structural Adaptations

The three main causes of a solitary kidney are birth defects, surgical removal of a kidney, and kidney donation. The consequence of having a SFK appears to depend on what stage in life the loss occurs, with loss during fetal life conferring a greater risk of future renal and cardiovascular disease than if the reduction in renal mass occurs during adulthood.

Loss of a kidney before the completion of nephrogenesis. The most common causes of a congenital SFK are unilateral renal agenesis (~1:500 births) or unilateral multicystic kidney dysplasia (~1:4,300 births) (81, 108). This solitary kidney undergoes compensatory growth and has on ultrasound been observed to increase in size from 20 wk of gestation, with a mean increase in length of ~11% by week 37 of gestation compared with age-matched controls (98). This raises the question as to whether this increase in renal mass is associated with enlargement of existing nephrons or an increase in the number of nephrons formed. In a single human case of congenital SFK, Maluf (50) reported an increase in both kidney weight (80%) and nephron number (56%), with no difference in glomerular size relative to the case control. From these observations, Maluf (50) proposed that growth of the congenital SFK was associated with an increase in nephron number rather than nephron enlargement. However, considering the ~12.8-fold variation in nephron number reported in the human kidney (10), this observation in a single case of congenital SFK...
should be viewed with caution. Nevertheless, in accord with this finding a study in 26-wk-old pigs born with a congenital SFK, without other overt anomalies, reported similar increases in remnant kidney weight (84%) and nephron number (50%) (97). However, since total glomerular volume was not lower, the renal growth in pigs born with a SFK was due to an increase in nephron number and size (97). Similarly, in a rat strain of unilateral renal agenesis Amakasu et al. (1) reported an increase in glomerular number (26%), albeit more modest, in the remnant kidney. In our model of fetal uni-x in the sheep, compensatory nephrogenesis, and with age nephron enlargement, was observed (this model is described in greater detail below) (22). Additionally, an increase in the number of glomerular capillaries per glomerulus has been documented following uni-x in neonatal rats (63). In contrast, glial cell line-derived neurotropic factor (GDNF) heterozygous mice born with unilateral renal agenesis had a 65% decrease in nephron number compared with wild-type mice (2 kidneys) (74). Thus GDNF, an important molecule in nephrogenic pathways, may play a positive role in other forms of renal agenesis in which compensatory nephrogenesis does occur. Collectively, these findings suggest that if the loss of a kidney occurs within the nephrogenic period, this does not lead to a 50% reduction in nephron number, as compensatory nephrogenesis occurs.

An Ovine Model of Congenital SFK

We have developed a fetal uni-x model in sheep. Importantly in the sheep the ontogeny of renal development is very similar to humans. The metanephric (permanent) kidney starts to develop at week 5 of gestation in humans (99) and in the sheep at day 27 of gestation (term 150 days) (55). Nephrogenesis continues into late gestation being complete in humans by week 36 of pregnancy and in sheep at day 130 of gestation (52). Thus nephron complement is determined before birth in both humans and in sheep (52). This is in contrast to many rodent species, where nephrogenesis is still ongoing after birth (17), and postnatal factors, such as the lactational period or reducing litter size at birth, are capable of affecting the final nephron complement (103, 104). In contrast, nephron maturation, including growth and differentiation of glomeruli and tubular segments, continues well into the postnatal period in all mammals (18). In our model of fetal uni-x, the kidney is surgically removed at 100 days of gestation (the beginning of the third trimester in humans) at which time point nephrogenesis is still very active (52). At ~130 days of gestation, the remaining kidney contained 45% more nephrons than a single kidney from a sham sheep, but compared with a sham-operated fetus with two kidneys the full nephron complement was reduced by ~30% (22). Correspondingly, remnant kidney weight was ~30% greater in the uni-x kidney compared with a single kidney from a sham sheep; however, total kidney weight was reduced in the uni-x sheep at 130 days of gestation (Fig. 1). Moreover, at this time (130 days of gestation) mean glomerular volume was significantly smaller in the uni-x compared with the sham animals, indicating that nephron enlargement is not a major early adaptation to loss of a kidney in utero (22). However, nephron enlargement does occur later; such that total kidney weight is normalized in the uni-x sheep by 6 mo of age (Fig. 1). It is interesting to note that while renal mass continued to increase with age in both groups, the total renal mass was greater in the sham group than in the uni-x sheep by 4 yr of age (Fig. 1), which suggests that compensatory growth may have reached an upper limit in the uni-x sheep. Overall this is a useful model in which to examine the functional consequences of being born with a SFK, with the compensatory growth similar to that occurring in humans born with unilateral renal agenesis.
However, it should be kept in mind that the surgical removal of a kidney from a fetus is unlikely to completely mimic the situation of a reduction in renal mass in humans in whom the loss of a kidney may be due to a genetic defect or an adverse intrauterine environment. On the other hand in a majority of animal models of low nephron endowment, the mother is exposed to an insult (undernutrition, glucocorticoids, etc.) that invariably affects the development of multiple fetal organs and systems, as well as the kidney (41). Importantly, the compensatory organ growth in response to fetal uni-x in our ovine model was specific to the kidney, as the weights of all other organs measured were similar between treatment groups at 130 days of gestation (22). Thus an advantage of the fetal uni-x model is that the impact of a reduction in renal mass can be studied in the absence of initial alterations in growth of other organs.

Loss of a Kidney After the Completion of Nephrogenesis

If a kidney is removed after the nephrogenic period, when no new nephrons can be formed, studies show that significant nephron enlargement occurs. However, it has also been consistently shown that the earlier in life that the nephron deficit occurs the greater the capacity for the renal compensatory response.

Compensatory renal growth in response to nephrectomy is a common finding in adult rodent models, leading to alterations in tubular sodium handling. Hayslett et al. (30) demonstrated an increase in lengths of proximal and distal tubules of 35 and 17%, respectively, in the remnant kidney in adult rats following uni-x. Other studies in rats have reported that the extent of compensatory renal growth is proportional to the amount of renal tissue that is surgically removed, where 50 and 70% renal ablation resulted in 81 and 160% increase in compensatory tissue growth in adult rats (40). Pollock et al. (66) also demonstrated an increase of ~72% length in the proximal tubules in adult rats 4–6 wk following uni-x, corresponding to a ~50% increase in proximal sodium reabsorption compared with the shams.

Lesson 1: the timing of the loss of a kidney has important consequences. Thus in summary, when a kidney is removed during the nephrogenic period, compensatory nephrogenesis occurs but nephron number is not fully restored. However, while nephron enlargement also occurs, this appears to develop after birth and to continue on, well into adulthood. In contrast, the compensatory growth following loss of a kidney after birth, when nephrogenesis is complete, is entirely due to nephron enlargement. However, this renal enlargement is relatively greater the earlier the loss of the kidney occurs in the postnatal period.

A Solitary Functioning Kidney: Adaptations in Basal Renal and Cardiovascular Function

Following Brenner et al. landmark publication in 1988 (14), a considerable amount of attention has been focused on the association between a low nephron endowment and the increased risk of developing hypertension and chronic kidney disease in adulthood. This increase in arterial pressure has been linked to the kidneys inability to maintain adequate sodium excretion (14).

Humans. Studies have revealed that a congenital renal mass reduction results in impaired renal function, with 50% of patients developing hypertension under the age of 18 yr (80), and 20–40% of these patients requiring dialysis by the age of 30 yr (77). Furthermore, Schreuder et al. (80) also demonstrated that individuals born of low birth weight have smaller kidneys and lower estimated glomerular filtration rate (GFR) and an even greater risk of developing cardiovascular diseases in adulthood. In contrast, a recent study found that children with a SFK at >5 yr follow-up had normal renal function and blood pressure, but microalbuminuria was markedly greater (84). The discrepancies between studies may reflect differences in sample size and the methodologies employed. However, a recent meta-analysis of studies examining unilateral renal agenesis (2,684 cases) found that 16% were hypertensive, 21% had microalbuminuria, and 10% had a GFR <60 ml·min⁻¹·1.72 m⁻² (102). Taken together, these findings indicate that individuals with a congenital SFK have a greater predisposition towards developing hypertension and renal dysfunction.

However, the loss of a kidney during adulthood in healthy subjects has not been associated with significant renal or cardiovascular disease in later life. A meta-analysis of studies in kidney donors (50% loss in nephron complement, n = 3,124) has shown that individuals undergoing adult nephrectomy are able to “tolerate” the loss of renal mass quite well, where despite an initial decrease in GFR, renal function remained stable over a 10-yr follow-up period (39). Another study revealed that while kidney donation (n = 5,048) resulted in a small increase in urinary albumin (indicative of single nephron hyperfiltration), there was no accelerated loss of renal function over a subsequent 15-yr follow-up period (27). This being said, Boudville et al. (13) demonstrated that a small ~5 mmHg increase in blood pressure occurred in kidney donors over a 5- to 10-yr postdonation period compared with age-matched control participants. At the present time, it appears that the modest rise in arterial pressure and urinary protein levels following adult kidney donation does not appear to be of sufficient magnitude to result in diagnosis of renal disease or hypertension amongst most donor populations (94). However, it can be argued that due to the extensive prescreening procedures before kidney donation, these donors represent a relatively healthy segment of the population and may not reflect individuals with preexisting health complications that may adversely affect outcomes to nephrectomy. Notably, there is concern that with the increasing demand for live organ donation that the stringent criteria for selection of organ donors are being relaxed. Indeed, Reese et al. (70) reported that a third of the donor population in the USA were either clinically hypertensive or obese or had a mild chronic renal disease.

If a kidney is removed in childhood, most commonly as a result of Wilm’s tumor or renal cancer, there are mixed reports regarding the long-term renal and cardiovascular outcomes. In children that underwent uni-x early in childhood, GFR remained stable for the following 20 yr (71). In another study, uni-x performed in later childhood for the treatment of Wilm’s tumor, after the completion of postnatal renal maturation (~2 yr of age), had minimal effects on blood pressure (11–28 yr post-uni-x) (49) and renal functional reserve (15 yr post-uni-x) (11). However, recently the results of the KIMONO study demonstrated that a SFK due to acquired kidney loss during...
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childhood compared with a congenital renal mass loss was associated with an even higher incidence of renal injury and hypertension (101). A relationship between small kidney length and renal dysfunction was identified leading to the suggestion that insufficient renal compensatory growth may be a marker for renal injury later in life. Further investigations are required to determine whether loss of a kidney in childhood is associated with the development of hypertension and renal disease.

Animal models of a SFK. Unilateral nephrectomy in neonatal rats on postnatal day 1 (when nephrogenesis is still ongoing in rodents) leads to the development of hypertension and impaired renal function by 20 wk of age in both male and female rats (105, 107). Similarly, a 30% congenital nephron deficit induced via fetal uni-x at 100 days of gestation in male sheep resulted in elevated arterial pressure, increased blood volume, and reductions in GFR and plasma renin activity (PRA) from as early as 6 mo of age (88). Moreover, renal dysfunction was also evident in younger uni-x sheep. Investigation of urinary function in the fetus at 4 wk after nephrectomy (130 days gestation) demonstrated that total urine flow and sodium excretion were half that observed in sham (2 kidney) fetuses; this suggests that despite the marked compensatory growth that has occurred by this age, urinary function had not undergone major adaptation at this stage (22). However, early signs of renal dysfunction were evident as urinary protein and creatinine levels were elevated in the fetuses with a SFK (22). Recently, microalbuminuria has also been documented in children with a solitary kidney (84). In uni-x lambs, at 3 mo of age marked disturbances in plasma creatinine, urea, and sodium levels indicative of disturbed extracellular fluid balance were also evident (88). In 6-mo-old male uni-x sheep, reductions in cardiac functional reserve that persisted with age were accompanied by left ventricular hypertrophy and reduced cardiac contractility by 24 mo of age (88). It was proposed that the increase in blood volume and hence arterial pressure observed in these uni-x animals at 6 mo of age was a result of enhanced sodium retention, pointing to impairments in sodium handling by the SFK in uni-x sheep (88). Notably, in uni-x sheep sodium excretion has been observed to be highly variable unlike sham animals (Fig. 2). In meal-fed male sham sheep at 6 mo of age, 24-h sodium excretion varied <5% in each animal over 6 consecutive days, whereas in individual uni-x sheep, sodium excretion rose and fell by as much as 30% over the 6-day period (Fig. 2). Similar fluctuations in daily sodium excretion have also been observed in female uni-x sheep at 5 yr of age (45). Thus renal function is impaired in animal models of SFK and is associated with hypertension, when the loss occurs during the nephrogenic period. Moreover, in animal studies it has been observed that, if a reduction in renal mass occurs in the early postnatal period when rapid renal growth and maturation is occurring, then hypertension also develops in adulthood (72).

Lesson 2: loss of a kidney in early life increases the risk of renal and cardiovascular disease. Renal function is reduced in subjects with a SFK that is acquired in the neonatal period, although the severity of this deficit has been offset by significant renal growth, leading to glomerular hyperfiltration. In animal models of congenital renal mass reduction, this renal deficit is clearly associated with adult hypertension. There is also evidence in humans that the congenital loss of a kidney results in hypertension, although this evidence is more limited, mainly due to the inherent difficulty in obtaining such data. Importantly, evidence from fetal uni-x sheep suggests that a SFK cannot tightly maintain ECF homeostasis as demonstrated by the marked daily fluctuations in sodium excretion despite a constant daily sodium and water intake.

A Solitary Functioning Kidney: Response to a Physiological Challenge

There is a paucity of information regarding how a person with a SFK responds to a physiological challenge that threatens ECF homeostasis. An acute saline load has been commonly employed as a physiological challenge to assess the ability of the kidney to regulate ECF homeostasis effectively. This approach has been used successfully to unmask deficits in renal function that were not apparent under resting conditions in essential hypertensives (48, 60, 67).

In our ovine fetal uni-x model, in response to an acute saline load, 6-mo-old male sham and uni-x sheep increased urine flow and sodium excretion (89). However, while the initiation of this increase in sodium excretion was delayed by ~90 min in uni-x sheep, the total sodium output over the duration of the study (210 min) was ~12% in excess of the infused load, compared with the sham group (89). Interestingly, when we physiologically challenged 5-yr-old female sheep with an acute saline load, neither the sham nor uni-x sheep were capable of excreting the complete volume of fluid (52 vs. 78%) nor the amount of sodium (40 vs. 68%) infused within the 3-h recovery period (44). While these cohorts of male and female sheep are not directly comparable, these findings are indicative of a loss in the functional capacity of the kidneys to respond to physiological challenges with advancing age, with this decline being exacerbated in animals born with a congenital nephron deficit. Collectively, our findings may have important clinical implications for individuals born with a SFK. Such individuals may be increasingly vulnerable to potential insults to the kidney, such as high dietary salt intake, obesity, and diabetes, given their limited capacity to respond to these secondary insults at older ages (59).

Fig. 2. Variation in daily sodium excretion. Six days of consecutive 24 h urinary sodium excretion measurements in 6-mo-old male sham (●; n = 6) or uni-x sheep (●; n = 5). Data are presented for individual sheep on each day of the 6-day measurement period and the line represents the average value (means ± SE) in that sheep.
The excretion of a saline load depends on the ability of the kidney to increase the filtered load of sodium and/or decrease the tubular reabsorption of sodium. The inability of younger male and older female uni-x sheep to tightly couple GFR to tubular reabsorption in response to a saline load was associated with enhanced gene expression of renal sodium transporters (NHE3, Na⁺/K⁺ ATPase α-, β-, and γ-subunits) and channels (ENaC-β and -γ subunits) within the uni-x kidney (44, 89). Indeed, Girardi et al. (28) demonstrated that uni-x in young rats resulted in an upregulation of NHE3 gene expression within the proximal tubules just 4 h post-unx.

Lesson 3: mismatching of the filtered load of sodium to tubular reabsorption. Subjects with a congenital SFK are likely to have a reduced capacity to respond to physiological challenges. The tubular growth and increased expression of ion transporter/channels in the renal tubules in uni-x sheep are linked to the increase in filtered load that each nephron must handle. However, it appears that the tight matching of filtered load to tubular reabsorption, which normally occurs in the excretion of ~1% of the filtered load of sodium in a kidney with a normal nephron complement, may not be as perfectly attuned in the setting of a SFK.

A Solitary Functioning Kidney: Mechanisms Underlying the Renal Dysfunction

The kidneys play an important role in the long-term regulation of ECF volume and thus arterial pressure (29). Many mechanisms contribute to the integrated renal response to changes in ECF volume and these enable the precise matching of excretion of sodium and water to intake.

Reduced contribution of the renin-angiotensin system. The renin-angiotensin system (RAS) is a powerful modulator of body fluid homeostasis and long-term blood pressure (65). The inability to effectively excrete a saline load in both younger male and older female uni-x sheep was accompanied by a blunted suppression of PRA (44, 89). Indeed, studies in low-renin essential hypertensives have also reported delays and reduced suppression of RAS components during saline loading, contributing to delays in diuresis and natriuresis (35, 67, 75). In contrast, many fetal programming models with a low nephron endowment have reported an upregulation of the intrarenal RAS components, leading to sodium retention and hypertension, due to the concerted actions of angiotensin II (ANG II) on the renal microvasculature and tubular sodium transport (54, 86, 106). However, fetal uni-x in sheep leads to a low-renin form of hypertension, with both 6-mo-old male and 5-yr-old female uni-x sheep showing significantly lower levels of renal renin and ANG II content, together with reduced renal gene expression of ANG II type 1 receptors (AT₁R) (91, 93). Therefore, while the systemic and intrarenal RAS is appropriately downregulated with regard to the elevation in arterial pressure, it is possible that this downregulation contributes to the reduced ability to rapidly regulate ECF volume in animals born with a congenital SFK. Importantly, we have recently reported that exogenous ANG II infusion in the presence of AT₁R blockade induced greater reductions in renal vascular resistance (RVR) and increases in renal blood flow (RBF) in 5-yr-old female uni-x sheep (91). The augmented rise in RBF and the decrease in RVR in response to ANG II infusion during AT₁R blockade suggested a greater stimulation of the ANG II type 2 receptors (AT₂R), as a result of a greater AT₂R-to-AT₁R ratio in 5-yr-old female uni-x sheep (91). Given that AT₁R expression and function are greater in females as opposed to males and that the AT₂R causes a leftward shift in the pressure-natriuresis relationship (32, 33), the AT₂R may be a potential therapeutic target for improving renal and cardiovascular function in subjects born with a congenital renal mass reduction.

Alterations in renal tubular sodium handling. Following unilateral nephrectomy, RVR decreases and RBF and GFR increases, at least in the adult rat (15, 31, 36). For GFR to rise following uni-x, when flow to the distal segments of the nephron concurrently increases, temporal adaptations in tubuloglomerular feedback (TGF) are likely to occur (12). Indeed, resetting of TGF has been demonstrated in lambs at birth, facilitating the postnatal increase in GFR and excretion by the kidney (16). Similarly, nephrectomy in adult rats also resets TGF operating point, to function at a higher single nephron GFR and solute delivery to the distal tubules (20, 57).

We have provided indirect evidence that TGF is altered in uni-x sheep. Uni-x male sheep at 6 mo of age had attenuated renal responses to furosemide infusion, a loop diuretic that via inhibition of NKCC2 cotransporters in the macula densa blocks TGF (92). While in the sham sheep there was a marked increase in urine flow, sodium excretion, and GFR in response to furosemide administration, these responses were significantly attenuated in the uni-x animals (92). Thus the attenuated renal hemodynamic and excretory responses to furosemide, in conjunction with a reduced ability to tightly regulate ECF homeostasis in response to saline loading (44, 89), are indicative of a suppression of TGF function in uni-x sheep. Enhanced sodium reabsorption within the uni-x kidneys (indicated by an upregulation of sodium transporters/channels) may indeed contribute to the resetting of the TGF mechanism to a lower sensitivity, increasing GFR until the NaCl delivery to the macula densa is “restored” towards normal (3). Furthermore, ANG II is a key modulator of TGF with increasing ANG II causing a leftward shift and decreasing ANG II causing a rightward shift of the TGF function curve (79). Hence, the suppression of the systemic and intrarenal RAS components maybe a contributing factor blunting the TGF response in uni-x sheep. Further studies are required to directly assess this hypothesis to gain more mechanistic insight into the perturbations associated with the regulation of renal function in models of congenital renal mass reduction.

Reduced urine concentrating capacity. In another study, Singh et al. (87) demonstrated that uni-x male sheep have marked deficits in urine concentrating ability from as early as 6 mo, with this defect exacerbated at 4 yr of age. This impairment was found to be mainly due to a reduction in the responsiveness of the collecting ducts to arginine vasopressin as a consequence of a reduced expression of the vasopressin type 2 receptors and aquaporin-2 water channels within the remnant kidney of uni-x sheep (87). Similarly, neonatal unilateral ureteral obstruction in rats, a model of renal insufficiency, results in impaired urine concentrating ability, which is accompanied with a reduced expression of aquaporin-2 water channels in the collecting ducts of the obstructed kidney (83). Moreover, a decline in urine concentrating ability has also been reported in humans (21) and rodents (51) with aging and is commonly used as an early marker for renal injury in young children with reductions in GFR (62).
Lesson 4: dysregulation of the renal mechanisms controlling ECF homeostasis. All the renal mechanisms regulating sodium and water balance that have thus far been investigated in the uni-x model of a congenital SFK in sheep are disrupted to some extent, including the RAS, TGF, vasopressin, and tubular sodium transport. Differentiating between the alterations in these systems that are driving the renal dysfunction and hypertension as distinct from those that are adapting in consequence will be important in determining prevention strategies.

A Solitary Functioning Kidney: Sex Differences

Premenopausal women are protected from cardiovascular disease compared with age-matched men (76). A case-controlled study of births with unilateral agenesis from 1,989–1998, reported a greater incidence of congenital SFK in male (59.4%) as opposed to female (40.6%) births (64). Another study also reported a male-to-female excess of 2.8:1 in the occurrence of renal agenesis in babies with a mean gestational age of 35 wk (82). While further evidence is required to determine if female sex is associated with better outcomes in children with a SFK, the available evidence suggest that this is likely (43).

Wood and colleagues (105, 107) using a model of uni-x in neonatal rats demonstrated that while both male and female uni-x rats developed hypertension, the degree of hypertension was greater in males. Furthermore, the onset of hypertension occurred earlier in male (8 wk) compared with female (20 wk) uni-x rats, with only male rats exhibiting an exacerbation in hypertension, proteinuria, and renal pathology at 20 wk (105, 107). Moreover, uni-x in adult rats has also demonstrated a sexual dimorphism in both the compensatory renal growth and the degree of glomerular and tubular damage occurring at 2 mo following uni-x (58). In that study, male rats demonstrated marked glomerular and tubular damage, while female rats exhibited only 50% of the compensatory renal growth observed in males, with no signs of kidney pathology (58). Rodríguez-Gómez et al. (72) reported that male rats appeared to be more sensitive to uni-x performed at 6 wk of age, compared with age-matched female counterparts. The male uni-x rats demonstrated an early onset of hypertension at 6 mo of age as opposed to 12 mo in the female rats, followed by greater exacerbation in hypertension reported in the males by 18 mo of age (72). Moreover, at 18 mo of age the compensatory renal hypertrophy following uni-x was markedly more severe in the male rats compared with the females (72). Collectively, these findings demonstrate that there is a sexual dimorphism in the structural and functional adaptations of the remnant kidney following uni-x, with the female sex conferring protection, which may have important clinical implications for prospective kidney donors.

In agreement with these findings, we have demonstrated that female uni-x sheep with intact ovaries do not develop hypertension until 2 yr of age (90). These results were in stark contrast to our observations in uni-x male (87, 88) and ovariec-tomized uni-x female sheep (53, 56) where hypertension developed from as early as 6 mo of age and was exacerbated with age. These findings strongly support a role for sex hormones in the sexual dimorphism evident in this model of congenital renal mass reduction. This being said, these sex differences in arterial pressure and hypertension disappear with aging, with the prevalence of hypertension in postmenopausal women being higher than in men (68). Although the specific mechanisms responsible for the increase in cardiovascular risk in women following menopause are currently unclear, several physiological mechanisms have been implicated such as, a decline in estrogen-to-androgen ratio, increases in PRA and endothelin, and reductions in the production/bioavailability of nitric oxide (NO) (34, 109).

Lesson 5: gender differences in outcomes. The risk of renal dysfunction and cardiovascular disease is greater in males than females born with a SFK. This protection in females, clearly demonstrated to be conferred at least, in part, by the sex-hormone estrogen, likely wanes with age.

A Solitary Functioning Kidney: Effect of Aging

There is extensive evidence demonstrating age-dependent declines in renal function due to both functional and structural changes (8), with both population-based and longitudinal studies revealing associations between reductions in GFR and increasing age (46, 73). In the population at large it has been estimated that ~4,500 nephrons per kidney are lost every year from 30 yr of age onwards (37). Certainly, in children born with a SFK, it has been reported that GFR starts to decline rapidly from the third decade of life, with ~20–40% developing end-stage renal disease in early adulthood (77).

In general, the age-dependent fall in renal function has been associated with decreases in renal plasma flow, alterations in the glomerular filtration barrier, and reductions in the number of functional glomeruli (37, 38, 73). Indeed in male sheep GFR declined significantly from 2 to 4 yr of age in the uni-x but not the sham-operated control sheep (87). In uni-x female sheep, despite no overt exacerbation of hypertension or a further decline in GFR, greater reductions in RBF and perturbations in the regulation of ECF homeostasis were observed at 5 yr of age (44, 90). The reduction in RBF in the uni-x female sheep with age was associated with an increase in renal vasoconstriction, and an increase in total peripheral resistance from 2 to 5 yr of age (90). Indeed, RVR increases with age and the increase is greater in hypertensive individuals (24, 78). The age-related decline in renal function has been reported to be more modest in women (9) and in female rats (4) than age-matched males. Moreover, ovariectomy in rats has been demonstrated to cause severe reductions in renal functional reserve and alterations in tubular handling of sodium with aging, with these effects being prevented by estrogen supplementation (61). These studies further emphasize the importance of estrogen in protecting females against the age-related decline in renal function, similar to that observed in our fetal uni-x model.

Role of NO in the aging kidney. NO plays a crucial role in the regulation of renal hemodynamics and sodium excretion in the kidney and is a major determinant of peripheral vascular tone, thus helping maintain ECF volume and arterial pressure (19, 42). A decrease in total NO production/bioavailability has been reported in animal models of chronic kidney disease (including renal mass reduction) and aging, contributing to a progressive loss of renal function (5, 6). Following a reduction in renal mass, the kidney undergoes both hemodynamic and structural changes. The hemo-
dynamic changes include an increase in RBF and a decrease RVR (15, 36). NO has been demonstrated to play a crucial role in mediating the increase in RBF via a reduction in RVR in the remnant kidney following nephrectomy (85). Moreover, NO is reported to be involved in maintaining renal hemodynamics and sodium homeostasis following uni-x in the adult rat, under both basal conditions (96) and in response to homeostatic challenges (2). Thus a deficiency in NO could result in vasoconstriction and reduction in RBF contributing to the development of hypertension.

There is also evidence of a sexual dimorphism in the NO system in younger adults, with premenopausal woman producing more NO than men (25). Moreover, female rats exhibit a greater renal expression of nitric oxide synthase (NOS) compared with males (69). These sex differences have been shown to be, in part, due to estrogen, which has several potent actions to stimulate NO production via enhancing endothelial and neuronal NOS expression and/or activity within the kidneys (7). For instance, a reduction in total NO production has been demonstrated with aging in male rats, contributing to the development of chronic kidney disease (23). Conversely, NO production remains unchanged in age-matched female rats resulting in protection from kidney injury (23). There is also evidence that renal NO levels are significantly lower in spontaneously hypertensive male rats compared with females (95). In our uni-x sheep with intact ovaries, RBF was reported to be similar between the uni-x and sham sheep at 1 yr of age (90). Thus blood flow to the remnant kidney in uni-x sheep was approximately double that reaching a single kidney of a sham animal, which may, in part, be due to an increase in NO production/bioavailability. Thus the decline in RBF in the intact uni-x female sheep at 5 yr of age may be indicative of a decrease in NO activity within the uni-x kidneys. Endogenously produced NO within the kidney also serves to buffer influences from a variety of vasoconstrictors, including ANG II and sympathetic nerves (26, 47). Thus the maintenance and progression of a higher vascular resistance in the remnant kidneys of uni-x sheep may, in part, be due to an increased inhibitory influence, underpinned by alterations in multiple systems involved in regulating extracellular fluid homeostasis (Fig. 3). There appears to be a sexual dimorphism in the functional adaptation of the remnant kidney following fetal loss of a kidney, with the female sex conferring protection at younger ages. However, with age this protection is lost, with both male and female uni-x sheep demonstrating age-related deterioration in cardiovascular and renal function, albeit more gradually in females. Thus individuals born with a SFK have reduced renal function that places them at future risk of renal and cardiovascular disease. Generally the age-dependent decline in renal function is sufficiently slow with no immediate threat in the absence of additional disease. This being said, the accelerated loss of renal function with age, may render these individuals with a SFK increasingly vulnerable to secondary insults.

Consequences of a loss of a kidney during early life

Fig. 3. Schema depicting the lifelong impact of losing a kidney during fetal life.

congenital renal mass reduction causes profound changes in the mechanisms that regulate renal function, contributing to renal dysfunction and hypertension in adulthood. Dysregulation of renal function in animal models born with a SFK are underpinned by alterations in multiple systems involved in regulating extracellular fluid homeostasis (Fig. 3). There appears to be a sexual dimorphism in the functional adaptation of the remnant kidney following fetal loss of a kidney, with the female sex conferring protection at younger ages. However, with age this protection is lost, with both male and female uni-x sheep demonstrating age-related deterioration in cardiovascular and renal function, albeit more gradually in females. Thus individuals born with a SFK have reduced renal function that places them at future risk of renal and cardiovascular disease. Generally the age-dependent decline in renal function is sufficiently slow with no immediate threat in the absence of additional disease. This being said, the accelerated loss of renal function with age, may render these individuals with a SFK increasingly vulnerable to secondary insults.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS


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