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A novel genetic model to explore the Brenner hypothesis: Linking nephron endowment and number with hypertension

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ABSTRACT

Nephron endowment, the total number of nephrons an individual is born with, is determined by both genetic and environmental factors during embryonic development. In 1988, Brenner hypothesized that there was an inverse relationship between nephron number and hypertension. Over the course of one's lifetime it is predicted that even healthy individuals will lose a significant percentage of nephrons as part of normal aging. Thus, a low nephron endowment at birth or in combination with age- or disease-related nephron loss could pre-dispose individuals to the development of hypertension. Currently, it is not clear what minimal number (ie, threshold) of nephrons is associated with susceptibility to glomeruli injury or hypertension, due in part to the lack of relevant animal models. The BPH2 mouse is a unique genetic model of hypertension that has a normotensive line (BPN3 mice) as well as a hypotensive line (BPL1 mice) derived from the original breeding of eight common inbred strains of mice. Thus, we hypothesize that the differences in blood pressure observed in BPH2, BPN3, and BPL1 mice will correlate inversely with nephron number as predicted by the Brenner hypothesis. If our hypothesis is true, then the BPH2 mouse model will provide a unique experimental model to study the impact of nephron endowment and nephron number on susceptibility to renal injury and hypertension.

Introduction

The nephron is both the basic structural and functional unit of the kidney [1]. Structurally, the nephron consists of the renal corpuscle, which includes the glomerulus and Bowman's capsule, and the renal tubule consisting of the proximal and distal convoluted tubules and the Loop of Henle. The function of the nephron is the filtration and reabsorption of water and electrolytes and secretion of wastes. Loss of functional nephrons such as that associated with disease, ie, diabetes, hypertension, and aging, can have a major impact on kidney function and blood pressure [2].

Nephron endowment refers to the total number of nephrons with which an individual is born, whereas nephron number is the total number of nephrons measured at any time post-birth [3]. As nephrogenesis is largely complete by 36 wks of gestation in humans, the maximum number of nephrons an individual will begin life with is determined during embryogenesis. In 1988, based on studies of nephron number in hypertensive patients, Brenner hypothesized that there is an inverse relationship between total nephron number at birth or over the course of one's life and the risk of developing hypertension [4]. Brenner also suggested that in order to limit any adverse changes in renal function related to reductions in nephron number residual nephrons compensate by increasing glomerular surface area (ie, glomerular hypertrophy). In the short-term glomerular hypertrophy serves as a mechanism to compensate for loss of functional nephrons, however such changes chronically contribute to the development of hypertension due to increased sodium and fluid retention, both of which result in increased extracellular fluid volume [4]. These changes then lead to a vicious cycle of increases in arterial and glomerular capillary pressure, glomerular hyperfiltration, injury and sclerosis, all of which can promote increases in arterial pressure (Fig. 1). Nephron number can also be influenced by diseases that directly affect the kidney such as hypertension, diabetes, and normal aging [5,6].

Early support for the Brenner hypothesis was provided by studies in which nephron number was found to be significantly lower in individuals previously diagnosed with hypertension as compared to nephron numbers in normotensive individuals [7–9]. While such studies are supportive of the Brenner hypothesis, there are also a number of studies in the literature, which have found no

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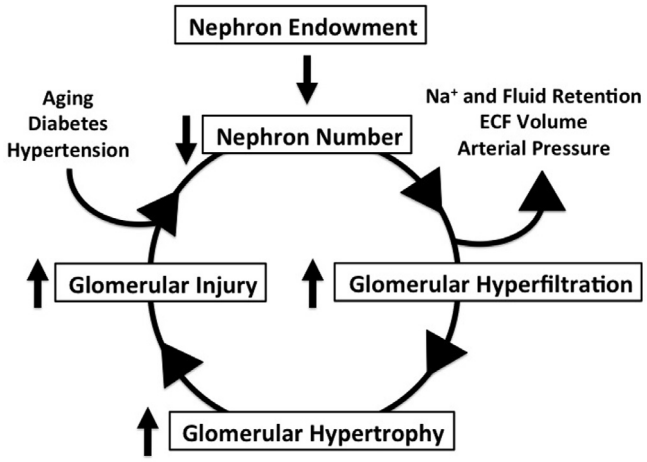

Fig. 1. Flowchart illustrating the mechanistic basis of the Brenner Hypothesis. Reductions in nephron number during embryogenesis, i.e. nephron endowment, promotes glomerular hyperfiltration, Na+ and fluid retention, increased extracellular fluid (ECF) volume, and increased arterial pressure. Glomeruli are thought to compensate for the reduction in nephron number by increasing glomerular surface area (i.e., glomerular hypertrophy). While glomerular hypertrophy is a positive short-term mechanism, glomerular hyperfiltration and hypertrophy in the long-term leads to glomerular injury and sclerosis both of which lead to further loss of functional nephrons. The vicious cycle of reduced nephron number, age-related nephron loss, and diseases that negatively impact the kidney can all serve to exacerbate nephron loss and promote additional increases in arterial pressure.

correlation between blood pressure and nephron number [10,11]. Some of the differences may be explained in part by methodological and technical limitations associated with measurement of nephron number in humans [12]. For example, there is little information directly correlating absolute blood pressure at the time measurement of nephron number as in most of the reported studies nephron number was assessed at autopsy following accidental death [4]. Also complicating measurements of nephron number in humans is that it is difficult to measure and track total nephron number in utero, at birth, and throughout an individual's lifespan in humans as there are few imaging modalities available to adequately assess fetal nephron endowment and post-natal nephron numbers in vivo [13,14]. Most reported measures of nephron number in humans also involve indirect measures of nephron number, such as kidney mass or volume [15]. Kidney biopsy is considered insufficient to make extrapolations to total nephron numbers as methods employing whole kidney provides the most accurate measurement of nephron number [15]. Due to the number of limitations associated with assessment of nephron number in humans, identifying new experimental models of reduced nephron number would allow for direct testing of the Brenner hypothesis and may reveal the impact of nephron endowment and nephron number on susceptibility to developing hypertension.

Experimental and genetic models of reduced nephron number

The most simplistic and straightforward experimental model of reduced nephron number is uninephrectomy or renal ablation [16–18]. Uninephrectomy produces a 50% reduction in nephron number and is associated with glomerular hypertrophy in the remaining kidney [16–18]. The effect of uninephrectomy on blood pressure is still debated as uninephrectomy is associated with little to no changes in arterial pressure in both human kidney donors and experimental animals [16–20]. In experimental animals uninephrectomy immediately after birth is associated with hypertension later in life whereas uninephrectomy in adulthood does not appear to be associated with any negative cardiovascular or renal outcomes [16,17].

In addition to uninephrectomy, there are several genetic models of unilateral renal agenesis (solitary kidney) that are also associated with reductions in nephron number of approximately 50% [21–24]. Although models of unilateral renal agenesis are associated with reductions of nephron number, most studies have found that the reduction in nephron number are associated with little to no changes in arterial pressure unless a second hit (eg high salt diet) is superimposed [24].

A number of mouse models of single gene deficiency have also been generated, which are associated with alteration in nephron number. For example, heterozygous deficient glial cell line-derived neutrophic factor ($GDNF^{+/-}$) mice have be found to possess 30% less nephrons than wild-type $GDNF^{+/+}$ mice [25,26]. GDNF is a key molecular signal in ureteric branching morphogenesis, which plays a primary role in nephron formation [27]. Indeed, the importance of GDNF expression was revealed with homozygous *GDNF* deficiency, which is neonatal, lethal [27]. While loss of a single *GDNF* gene is associated with a marked reduction in nephron number, surprisingly heterozygous *GDNF* deficiency has little to no effect on blood pressure under baseline conditions, although $GDNF^{+/+}$ mice but not wild-type mice do become hypertensive when fed a high salt diet [25,26,28].

Conditionally-targeted fibroblast growth receptor 2 deficient ($FGFR2^{-/-}$) mice have been reported to have 24% less nephrons than wild-type $FGFR2^{+/+}$ mice [29]. Although the reduction in nephron number is slightly less than that observed in $GDNF^{+/-}$ mice, *FGFR2* deficiency is associated with a 20 mmHg higher level of systolic blood pressure compared to wild-type $FGFR2^{+/+}$ mice [29]. FGFR2 also plays a crucial role in nephron development, as *FGFR2* deficiency results in abnormal uteric branching and renal hypoplasia [30]. Conditional $FGFR2^{-/-}$ mice develop normal appearing nephrons and tubules, however they develop less overall nephrons [30]. $FGFR2^{-/-}$ kidneys are also characterized by inappropriate apoptosis, most likely a contributing factor to the smaller kidney mass in these mice [30].

In an example of a mouse model of enhanced nephron number, tumor growth factor beta ($TGF\beta^{+/-}$) mice have 60% more nephrons at postnatal day 30 compared to wild-type mice [31,32]. In the developing kidney TGFβ normally limits uteric duct branching and elongation, thus the reductions in TGFβ expression result in greater branching and more total nephrons. Although $TGF\beta^{+/-}$ mice might be predicted to have lower blood pressures, blood pressure in $TGF\beta^{+/-}$ mice was found to be similar to wild-type mice [31,32]. Interestingly, having more nephrons confirms protection against hypertension as $TGF\beta^{+/-}$ mice, unlike wild-type mice, do not develop hypertension in response to a high salt diet [32].

Even though $GDNF^{+/-}$, conditional $FGFR2^{-/-}$, and $TGF\beta^{+/-}$ mice display alterations in nephron number that may or may not directly impact blood pressure, it is important to note that these are all examples of single gene defects. While the genetically-altered models highlighted clearly demonstrate the influence of specific genes on nephrogenesis, it is difficult to compare and contrast differences in nephron number between the various models developed on distinct genetic backgrounds [25,29,31]. Genetic background in mice is known to influence a number of phenotypes, including blood pressure and renal injury [18,33–35]. Thus, we propose to examine the Brenner hypothesis using BPH2 (blood pressure high) mice, a genetic model of hypertension with all phenotypically diverse blood pressure lines (ie hypertensive, normotensive and hypotensive mice) derived from the same original genetic stock, thus making comparisons between lines possible [36].

BPH2 mouse model of genetic hypertension

BPH2 mice were generated by Schlager in 1974 through selective breeding of eight common inbred mouse strains [36]. The eight