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Review

Biochemical basis for pharmacological intervention as a reprogramming strategy against hypertension and kidney disease of developmental origin

You-Lin Tain [a,b], Samuel H.H. Chan [b], Julie Y.H. Chan [b,*]

[a] Department of Pediatrics, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung 833, Taiwan
[b] Institute for Translational Research in Biomedicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung 833, Taiwan

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ABSTRACT

The concept of "developmental origins of health and disease" (DOHaD) stipulates that both hypertension and kidney disease may take origin from early-life insults. The DOHaD concept also offers reprogramming strategies aiming at shifting therapeutic interventions from adulthood to early life, even before clinical symptoms are evident. Based on those two concepts, this review will present the evidence for the existence of, and the programming mechanisms in, kidney developmental programming that may lead to hypertension and kidney disease. This will be followed by potential pharmacological interventions that may serve as a reprogramming strategy to counter the rising epidemic of hypertension and kidney disease. We point out that before patients could benefit from this strategy, the most pressing issue is for the growing body of evidence from animal studies in support of pharmacological intervention as a reprogramming strategy to long-term protect against hypertension and kidney disease of developmental origins to be validated clinically and the critical window, drug dose, dosing regimen, and therapeutic duration identified.

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Contents

1. Hypertension and kidney disease of developmental origin: evidence from human and animal studies . . . 00
2. Common mechanisms that underlie programmed hypertension and kidney disease . . . 00
   2.1. Renin-angiotensin system . . . 00
   2.2. Oxidative stress . . . 00
   2.3. Autophagy . . . 00
   2.4. Epigenetic regulation . . . 00
   2.5. Glucocorticoid . . . 00
   2.6. Nutrient-sensing signals . . . 00
3. Pharmacological intervention as a reprogramming strategy . . . 00
   3.1. Blockade of the RAS . . . 00
   3.2. Antioxidants . . . 00
   3.3. Melatonin . . . 00
   3.4. Resveratrol . . . 00
   3.5. Statins . . . 00
   3.6. Others . . . 00
4. Conclusions . . . 00

* Corresponding author at: Institute for Translational Research in Biomedicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung 83301, Taiwan.
E-mail addresses: tainyl@cgmh.org.tw (Y.-L. Tain), shhchan@cgmh.org.tw (S.H.H. Chan), jchan@cgmh.org.tw (J.Y.H. Chan).

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1. Hypertension and kidney disease of developmental origin: evidence from human and animal studies

Hypertension and kidney disease affect millions of people across the globe, with many adolescents at risk at an early age. Despite recent advances in pharmacotherapy [1,2], the global prevalence of hypertension and kidney disease remains on the rise, and the age of onset becomes younger. Of note is that, in addition to sharing many common risk factors, hypertension and kidney disease could be the cause and consequence of each other. Thus, hypertension is a major risk factor for kidney disease, whereas chronic kidney disease (CKD) is the most common form of secondary hypertension. More importantly, following the concept of "developmental origins of health and disease" (DOHaD) [3,4], both disorders may take origin from early-life insults.

Blood pressure (BP) is regulated by a complex process that includes major contributions from the kidney. The developing kidney, in turn, is vulnerable to adverse early-life environments. According to the DOHaD concept, adverse environments during critical periods of kidney development may produce long-term effects on the structure and/or function of the kidney. This process, known as renal programming [5,6], can increase the risk of hypertension and kidney disease later in life. The DOHaD concept also offers reprogramming strategies aiming at shifting therapeutic interventions from adulthood to early life, even before clinical symptoms are evident [7].

Based on the two aspects of the DOHaD concept, this review will first present the evidence for the existence of, and the programming mechanisms in, kidney developmental programming that may lead to hypertension and kidney disease. This will be followed by potential pharmacological interventions that may serve as a reprogramming strategy to counter the rising epidemic of hypertension and kidney disease.

Barker and colleagues [8] were the first to demonstrate in their seminal work the association between low birth weight (LBW) and the increase in risks of hypertension. Studies of twin pregnancies further revealed a positive association between LBW and high BP in the twin infants [9]. Subsequent lines of evidence confirmed the DOHaD concept by showing a positive correlation between adverse early-life environments and the development of adult disease in later life [10–12]. In particular, offspring exposed to severe famine during pregnancy are more prone to develop a variety of adult disorders, including hypertension and kidney disease [13,14]. Another support for the DOHaD concept arises from mother-child cohort studies. As reviewed elsewhere [7], risk factors, including small gestational age, short-term breastfeeding, low vitamin D intake, smoking, gestational hypertension, maternal obesity, and excessive postnatal weight gain, have been associated with developmental programming of hypertension and kidney disease in several mother-child cohorts. In addition, epidemiological studies substantiate the notion that LBW and prematurity are risk factors for hypertension and kidney disease in later life [4,15]. A meta-analysis of more than two million individuals reported that those with LBW had a 70% increased risk for the development of CKD [16]. However, epidemiological studies could not establish a direct cause-and-effect relationship between insults and subsequent adult diseases in human and clarify the molecular mechanisms that underlie the expressed phenotype.

Animal models in which a single pathology can be established and studied in detail provide a clear advantage for elucidating the types of insults that drive disease programming, identifying the critical window of vulnerability, understanding the potential mechanisms, and developing reprogramming strategies. More importantly, differences in life expectancy (up to 60–80 years in humans, 10 years for sheep, and 2–3.5 years for rodents) across species afford animal models an attracting approach to understand the mechanisms of and specific outcomes from developmental contribution to adult chronic diseases, including hypertension and kidney disease.

Emerging evidence from animal studies confirms the association between early-life insults, renal programming, and developmental programming of hypertension and kidney disease in later life. As shown in Fig. 1, maternal malnutrition, over-nutrition, perinatal hypoxia, diabetes, environmental chemicals, toxins, and medication have all been reported to affect kidney development and contribute to developmental programming of hypertension and kidney disease [4–7,17].

About 30 years ago, Brenner et al. [18] hypothesized that low nephron endowment is a risk factor for adult hypertension and kidney disease. As we reviewed previously [19], a number of early-life insults, including maternal diabetes [20], maternal drug use [21], maternal ethanol intake [22], maternal malnutrition [23], maternal iron deficiency [24], and antenatal glucocorticoids exposure [25,26], may act as causal contributors. The main phenotype of renal programming associated with reduced nephron endowment is glomerular hypertrophy [15,18]. A reduction in nephron number in the absence of compensatory hypertrophy would be expected to cause a decrease in glomerular filtration rate. At the same time, reduced nephron numbers might increase the susceptibility to development of hypertension and renal dysfunction in response to additional environmental insults and kidney injury in later life. Nevertheless, low nephron endowment per se does not exist in all animal models of hypertension and kidney disease of developmental origins. Nephron number can be unaltered [27], or even increased in response to renal programming [28,29]. Thus, low nephron endowment could most likely be one of several mechanisms by which renal programming leads to hypertension and kidney disease.

2. Common mechanisms that underlie programmed hypertension and kidney disease

Despite the diversity in early-life insults, emerging evidence from animal studies indicates the existence of several common pathways that may contribute to the pathogenesis of hypertension and kidney disease of developmental origin. These include at least the renin-angiotensin system (RAS), oxidative stress, autophagy, epigenetic regulation, glucocorticoid effect, and nutrient sensing signals [4–7,30].

2.1. Renin-angiotensin system

The RAS, a well-recognized key regulator of BP and renal functions, plays a critical role in DOHaD [31,32]. The classical RAS, defined as the angiotensin converting enzyme (ACE)-angiotensin (Ang) II-angiotensin type 1 receptor (AT1R) axis, promotes

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