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ORIGINAL ARTICLE

Differential modification of enalapril in the kidneys of lean and 'programmed' obese male young rats

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Summary
Objective: We investigated whether enalapril treatment could have beneficial effects on nutritionally-programmed renal changes in postnatally overfed young rats.
Methods: Three or 10 male pups per mother were assigned to either the Obese or Lean groups during the first 21 days of life. These pups were treated with enalapril (Obese enalapril, OE; Lean enalapril, LE) or vehicle (Obese control, OC; Lean control, LC) between 15 and 28 days. All pups had their kidneys examined at 29 days.
Results: OC pups weighed more than those in the LC group between 7 and 28 days of age ($P < 0.05$). Enalapril reduced body weights in rats from both the Obese and Lean groups between 22 and 28 days ($P < 0.05$). Renal cell proliferation and apoptosis, glomerulosclerosis, and tubulointerstitial fibrosis were all increased by enalapril ($P < 0.05$). Among the groups, renal cell apoptosis and serum creatinine were the highest in OE pups ($P < 0.05$). Enalapril treatment resulted in contrasting molecular expression profiles involved in renal maturation and repair in the kidneys of the rats from the Lean and Obese groups.
Conclusion: Enalapril can differentially modulate renal molecular alterations in lean and postnatally overfed rats and may be not beneficial in obese young male rats.

Introduction

Substantial studies have shown the kidney's sensitivity to adverse perinatal environments can cause permanent changes in renal structure and function

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[1—3]. These programming events may manifest grossly as reduced renal mass, or more subtly as altered activity of the renal renin—angiotensin system (RAS) [2]. Indeed, we recently have demonstrated that alterations in the RAS can contribute to altered renal growth and eventual renal impairment in rats exposed to early postnatal overnutrition [4—6]. Inappropriate stimulation of the RAS was also accompanied by increased cellular turnover and inter-ventricular septal hypertrophy in the hearts of neonatally overfed juvenile rats [7].

Importantly, all components of the RAS are highly expressed in the developing kidney and an intact RAS is pivotal for normal renal development [8]. Inhibiting neonatal RAS causes the underexpression of genes important to the cytoskeleton and extracellular matrix (ECM) of the developing kidney, leading to inadequate matrix assembly and abnormal cell—cell and cell—matrix interactions [9]. The tubular cells of the kidney undergo apoptosis when deprived of cell—cell and cell—matrix adhesion [10], which is significant given that the inappropriate regulation of apoptosis has been shown to impact nephrogenesis [11]. It is therefore expected that the ECM plays a vital role during kidney development and repair, and may recapitulate part of the genetic program involved in renal development to restore proper tissue function after damage [12]. Matrix metalloproteinases (MMPs), tissue inhibitor of MMPs (TIMPs), and plasminogen activator inhibitor (PAI)-1 are known to be the major regulators of ECM synthesis and degradation [11].

High RAS activity is frequently observed in obese individuals and angiotensin converting enzyme (ACE) inhibition has been shown to have nephroprotective effects in obese patients with chronic kidney disease [13]. In obese Zucker rats, the late inhibition of RAS not only halts the progression of several markers of renal injury, but even induces a partial regression of glomerular damage [14]. Recent studies also suggest that RAS inhibition reduces body weight and fat in a diet-induced model of obesity in the rat [15,16]. This suggests that reducing RAS activity could be beneficial in treating obesity and obesity-related morbidities as well.

Further studies are still necessary for elucidating the influence of neonatal nutrition on long-term renal disease and steps to avoid obesity and nutrition-related chronic diseases should start early in life [17]. Our recent studies have shown that postnatal overnutrition during an early period of life can induce persistent overweight into adulthood and life-long renal alterations in male rats [4—6]. Overweight and dysregulation of the intra-renal RAS and ECM-related molecules were observed at one month of age [4]. Thus, the present study aimed to investigate that early ACE inhibition after the nephrogenic period can ameliorate an increase in body weight and renal pathologic changes induced by postnatal overnutrition at an early point of established renal alterations. The hypothesis is that enalapril treatment after the completion of nephrogenesis has protective effects on kidney structure and short term function of postnatally overfed rat pups. To investigate this, rapid postnatal growth and subsequent obesity were induced in these rats by early postnatal overnutrition over a 28-day period. The ACE inhibitor enalapril was then given to the rats between 15 and 28 days in order to study the effects of ACE inhibition on nutritionally-programmed renal changes.

Materials and methods

Animal preparation

Virgin Sprague Dawley rats were timed mated with normal males at the age of three months. On the second day of life, male pups were randomly distributed among the mothers to achieve cross-fostering. The newborns were divided into litters of 10 that would receive normal feeding (the ''Lean'' group, $n = 60$) or litters of three that would be induced to overfeed (the ''Obese'' group, $n = 36$). At 15 days of age, the offspring in the Lean and Obese groups were further divided into two, with subsets of each group either receiving 30 mg/kg of enalapril dissolved with water (Lean enalapril group, LE, $n = 30$; Obese enalapril group, OE, $n = 18$) or the same amount of vehicle (Lean control group, LC, $n = 30$; Obese control group, OC, $n = 18$). This dose of enalapril is known to block the effects of angiotensin II [18]. Enalapril or vehicle was administered via an orogastric tube to pups between 15 and 28 days, a period of time after the completion of nephrogenesis. The rats were weaned at 21 days of age and then were given free access to tap water and standard laboratory chow (Purina, Cargil Agri Purina, Inc., Jeolla-do, South Korea). Body weights were monitored every three days from 1 to 28 days of life. Rats were sacrificed at 29 days with their kidneys harvested and processed for the study. All experimental procedures were approved by the Animal Experimentation Ethics Committee of the Korea University Guro Hospital. All procedures conformed to the Korean national guidelines for the care and