SEX DIFFERENCES IN RENAL TRANSCRIPTOME AND PROGRAMMED HYPERTENSION IN OFFSPRING EXPOSED TO PRENATAL DEXAMETHASONE

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OBJECTIVES

1. Prenatal dexamethasone (DEX) exposure induced programmed hypertension in adult offspring.
2. We examined whether prenatal DEX-induced programmed hypertension is in a sex-specific manner.

METHODS

1. Dexamethasone (0.1 mg/kg body weight) or vehicle was intraperitoneally administered to pregnant SD rats from gestational day 16 to 22. Offspring were assigned to 4 groups (n = 7-8/group): male control (MC), female control (FC), male DEX (MD), and female DEX (FD). Rats were killed at 16 weeks of age.
2. Blood pressure was measured in conscious rats by an indirect tail-cuff method.
3. Components of the RAS and sodium transporters were analyzed by qPCR.
4. Kidney samples (n=3/group) were used for RNA next-generation sequencing (NGS).

Table 1. Weights and functional parameters

	Male		Female		Statistics		
	Control	DEX	Control	DEX	P_{Sex}	P_{Dex}	P_{INT}
Mortality	0%	0%	0%	0%			
Body weight (BW) (g)	510±13	493±20	276±8	273±7	<0.001	0.464	0.571
Left kidney weight (g)	2.0±0.07	1.7±0.09	1.2±0.04	1.04±0.04	<0.001	<0.001	0.279
Left kidney weight/ 100g BW	0.40±0.01	0.35 ± 0.01	0.45±0.02	0.38±0.01	0.004	<0.001	0.603
Systolic blood pressure (mmHg)	155±3	163 ±3	147±4	149±4	0.006	0.162	0.48
Diastolic blood pressure (mmHg)	71±3	82±4	74 ±2	79±3	0.9	0.026	0.337
Mean arterial pressure (mmHg)	99±3	109±3	99±1	102±2	0.144	0.011	0.272

Values are means ± SEM. N=8 per sex in control group. N=7 per sex in dexamethasone (DEX) exposure group. Data were analyzed by two-way ANOVA. Significant results are highlighted in bold.

RESULTS

1. Prenatal DEX induced sex-specific increase in BP in male but not female adult offspring (Table1; Figure 1).
2. A total of 90 and 93 sex-biased DEGs were identified in control and DEX exposure offspring, respectively (Figure 2).
3. The resistance of female offspring to prenatal DEX-induced programmed hypertension is related to a lower *Agt* mRNA expression and higher AT2R protein level (Figure 3)

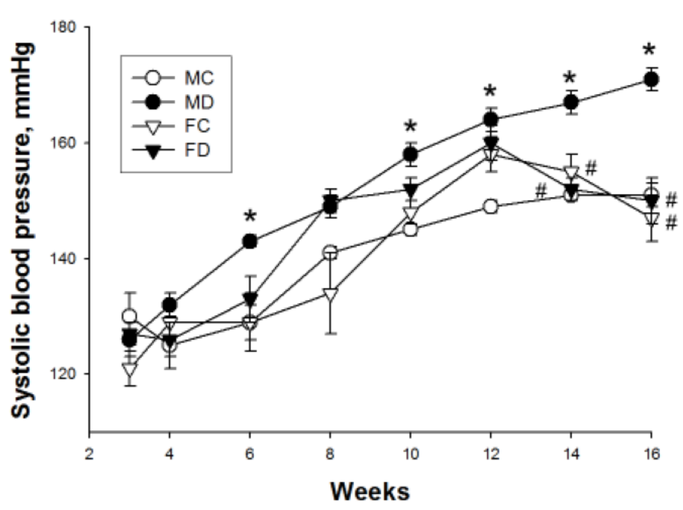
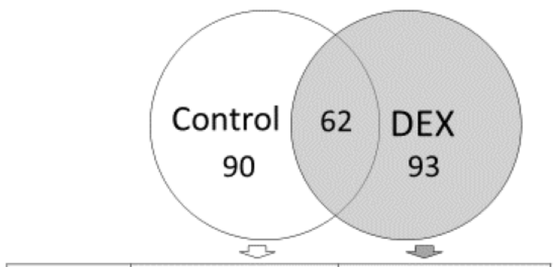


Fig. 1. Effects of prenatal dexamethasone exposure (DEX) on SBP. N=7-8/group. *P<0.05 vs. MC; #P<0.05 vs. MD.



Sex Biased Genes	Male > Female: 53 genes	Male > Female: 41 genes
KEGG Pathway	Drug metabolism, Metabolism of xenobiotics by cytochrome P450, Retinol metabolism, PPAR signaling pathway, Glycosaminoglycan degradation	Drug metabolism, Metabolism of xenobiotics by cytochrome P450, Retinol metabolism, Glycosaminoglycan degradation

Fig. 2. Venn diagram depicting unique and shared (overlapping circles) sets of differential expressed genes (DEGs) of males vs. females between control (white circle) and prenatal dexamethasone exposure (DEX, grey circle).

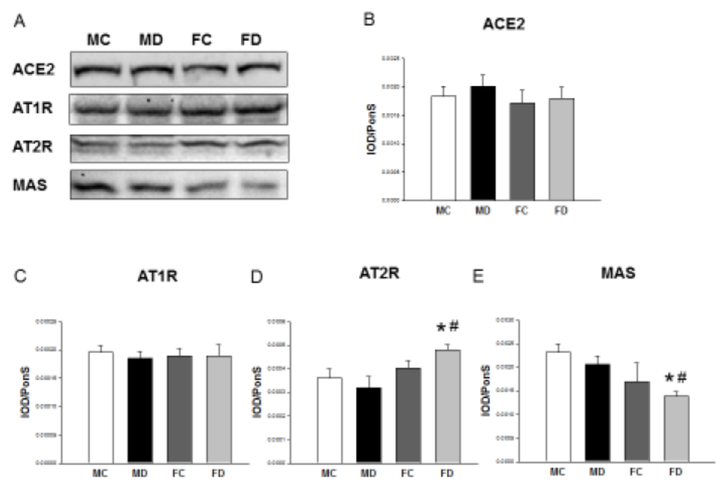


Fig. 3. Representative Western blots (A) show ACE2 (90 kDa), AT1R (41 kDa), AT2R (50 kDa), and MAS (37 kDa) in offspring kidney at the age of 16 weeks. Relative abundance of renal cortical (B) ACE2, (C) AT1R, (D) AT2R, and (E) MAS. N = 7-8 for each group. *P<0.05 vs MC. #p<0.05 vs MD.

CONCLUSIONS

1. Prenatal DEX induced programmed hypertension, which was confined to male adult offspring. However, prenatal DEX induced long-term alterations of renal transcriptome in both sexes.
2. Our NGS data identified *Hbb* and *Hba-a2* related to DEX-induced programmed hypertension. In addition, a number of sex-biased genes might elicit programmed changes in response to prenatal DEX exposure.
3. By exploring the sex-dependent underlying mechanisms to prenatal DEX-induced renal programming, we might develop novel deprogramming strategy to prevent programmed hypertension in premature baby receiving corticosteroids in both sexes.

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