Adrenal gland functioning in male and female offspring from Dx treated mothers

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1. Introduction

The organization and functioning of the hypothalamic-pituitary-adrenal (HPA) axis are highly conserved throughout mammalian phylogeny. There is a marked diurnal rhythm of HPA axis activity with peak levels proceeding the active part of the day in order to optimize energy mobilization and distribution. During the stress response, as the consequence of the HPA axis activation and increased adrenal glucocorticoid circulating level, energy usage is directed to promote survival [1].

The basic functioning as well as the stress response of the HPA axis show a clear sex-specific pattern. There are significant differences in the adrenocortical glucocorticoid release, caused by diverse real or anticipated situations that disrupt homeostasis, comparing males and females. The male or female gonadal hormones influencing hypothalamic neurons, mainly CRH synthetizing neurons, pituitary hormone producing cells, primarily ACTH cells, as well as adrenocortical steroidogenic cells, determined those differences [1]. The functioning of monoamine neurotransmitters that control HPA axis responses to acute and chronic stress in sex specific manner contributes to these differences [2].

Prenatal life experiences also have a significant impact on postnatal HPA axis functioning determining sexually dimorphic responses [3]. Exposures to excessive levels of maternal glucocorticoids signalize adverse environmental conditions for the developing fetus so the developmental trajectory must be adjusted to the expected postnatal surroundings. The application of synthetic glucocorticoids during gestation had similar effect on the developing fetus i.e. maturation of numerous tissues was promoted in parallel with growth retardation that occur causing permanent changes in the endocrine milieu [3].

The aim of this study was to determine eventual sex specific dexamethasone (Dx) programming effects of rat pituitary-adrenal (PA) axis examining offspring, after fetal glucocorticoid overexposure. Thus, the activity of the PA axis was considered in adult, 90 days old male and female offspring, from control and Dx treated mothers during pregnancy. To that end, stereological parameters of the adrenal gland, as final effector of the HPA axis, as well as ACTH circulating level, aldosterone and corticosteroid output from adrenal gland, were investigated.

2. Details of experiment

Thus gravid females were exposed to multiple doses of synthetic glucocorticoid dexamethasone (Dx) during 16-19 days of pregnancy (3x0.5mg/kg/b.m. Dx; 16th-18th gestational day). The activity of the PA axis was considered in 90 day old male and female rat offspring from control and Dx-treated dams. The adrenal glands from both groups were subject to histological and stereological analyses. In addition, concentrations of circulating hormones as ACTH, corticosterone and aldosterone were determined with chemiluminescence method and enzyme immunoassay, respectively.

3. Results

In males, the body mass was significantly increased, while adrenal gland weight and relative adrenal gland weight were significantly decreased in comparison to females. Dx exposure during pregnancy markedly decreased adrenal gland weight and relative adrenal gland weight in female offspring compared to the control group; in male offspring, the maternal Dx treatment did not provoke any changes to the examined parameters in relation to the control values (Table 1).

Table 1. Body mass, adrenal gland weight and relative adrenal gland weight from 3-month-old female and male offspring of control and Dx treated mothers.

	Body mass (g)		Absolute adrenal gland weight (g)		Relative adrenal gland weight (%)	
	Female	Male	Female	Male	Female	Male
C	198 ± 11	274 ± 15*	32.2 ± 2.1	27.8 ± 1.7*	16.2 ± 0.9	10.1 ± 0.8*
Dx	193 ± 8	277 ± 17*	26.3 ± 2.2[a]	25.1 ± 2.1	13.6 ± 1.0[a]	9.1 ± 1.2*

All values are provided as the mean ± SD; n=6. * $p<0.05$ *vs*. female; [a] $p<0.05$ *vs*. C.

The histological analysis and stereological measurement revealed that the volume of the male adrenal gland is markedly smaller in relation to the female volume ($p<0.05$) (Figure 1). Dx exposure during pregnancy significantly decreased ($p<0.05$) the volume of the female adrenal gland, while significant differences were not present in males (Graph 1).

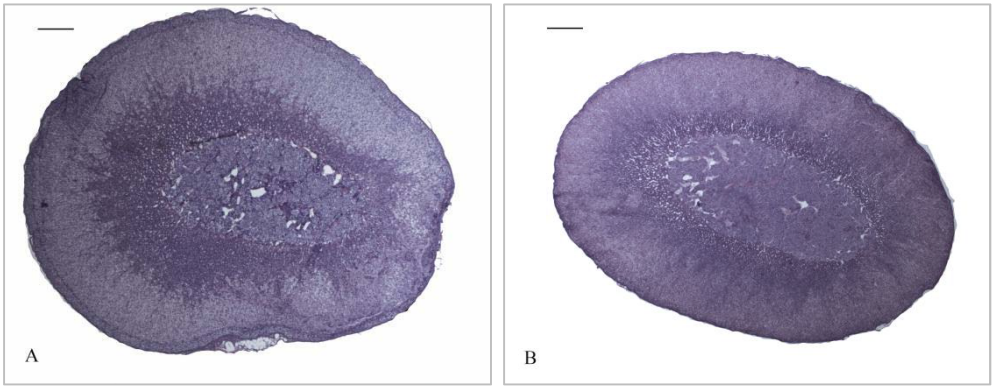
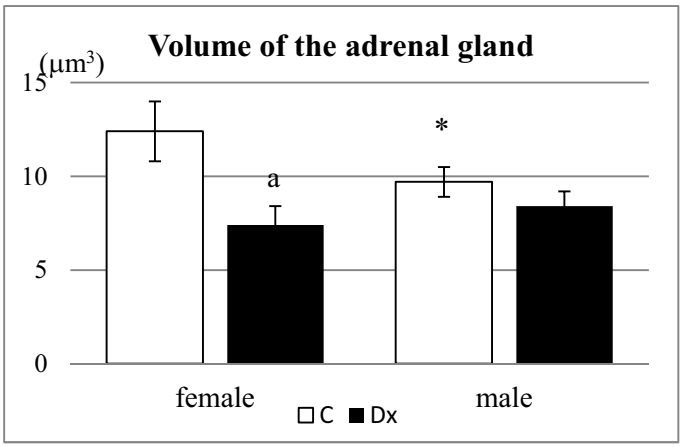


Figure 1. By comparing the central sections of the adrenal gland of the females (A) and males (B) differences in the size become clearly visible. Bar 400 µm.

Graph 1. Volumes of the male and female adrenal gland in offspring from control (C) and Dx-treated (Dx) dams.



All values are provided as the mean ± SD; n=6. * $p<0.05$ *vs*. female; [a] $p<0.05$ *vs*. C.

In comparing female and male basal plasma ACTH concentration, significant differences were not established. Prenatal Dx exposure provoked marked elevation of the ACTH level in females in relation to control values, while there was no difference in male offspring. Corticosterone circulating concentration was significantly higher in females compared to males. Dexamethasone treatment of gravid females did not have a significant effect on the corticosterone concentration in both females and males compared to their respective control values. Comparing aldosterone concentration between female and male control rats significant decrease was determined in males. Dx exposure did not significantly change the aldosterone circulating level neither in females nor males (Table 2).

Table 2. Results of hormonal data in 3-month-old female and male offspring of control and Dx treated mothers.

	ACTH (pg/mL)		Corticosterone (ng/mL)		Aldosterone (ng/mL)	
	Female	Male	Female	Male	Female	Male
C	21 ± 4	25 ± 4	26 ± 4	15 ± 6 * ↓	0.109 ± 0.014	0.069 ± 0,009 *↓
Dx	31 ± 7 [a] ↑	28 ± 4	32 ± 4	23 ± 8	0.096 ± 0.007	0,075 ± 0,007

All values are provided as the mean ± SD; n=6. * $p<0.05$ *vs*. female; [a] $p<0.05$ *vs*. C.

3. Conclusions

Results of PA morphofunctional study revealed that under basal conditions, females have greater adrenal gland secretory ability due to increased adrenal weight, adrenal volume and circulating concentrations of adrenocortical hormones, corticosterone and aldosterone, in relation to males. Sex-specific programing effects after prenatal Dx exposure were pronounced in female offspring, where higher activity of the PA axis was observed after the hormonal study and adrenal gland stereological analysis; more precisely, in females, the increased ACTH forced adrenal gland synthetic activity, resulting in a corticosterone concentration as in control, reached by adrenal glands that have a reduced volume. Maternal Dx treatment did not change the hormonal output of the PA axis and adrenocortical volume in male offspring under basal conditions.

4. References

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