Sexually dimorphic effects of maternal alcohol intake and adrenalectomy on left ventricular hypertrophy in rat offspring

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HUMAN EPIDEMIOLOGICAL STUDIES have linked low birth weight with increased emergence later in life of cardiovascular and metabolic pathologies, including ischemic heart disease, hypertension, insulin resistance, and non-insulin-dependent diabetes (3, 4, 6, 7, 69). These observations have led to the hypothesis that changes in the fetal environment produce physiological adaptations by the fetus that lead to small birth weight. Meanwhile, the net effect of these changes, while beneficial before birth, may produce adverse outcomes in the long term. These adaptations are called fetal programming. Among other challenges to the fetal environment, altered maternal nutrition, such as protein or iron deficiency, modifies or programs fetal and adult morphology as well as metabolic and endocrine pathways (6, 5, 24).

One consistent feature of numerous human epidemiological studies and animal models of low birth weight is prenatal exposure to glucocorticoids (10, 36, 66). Furthermore, even brief prenatal exposure to elevated glucocorticoids can result in permanent adverse changes in the adult offspring’s cardiovascular system (13, 32). Although glucocorticoids are important in normal development, excessive exposure through administration of glucocorticoids to the mother leads to reduced birth weight (67). However, decreased levels of maternal plasma corticosterone (Cort) by maternal adrenalectomy also result in reduced birth weight, and very low levels of Cort are sufficient to normalize birth weight and increase fetal Cort levels (51). As fetal adrenals start functioning during the last week of gestation (16), maternal glucocorticoid levels are the primary regulators of fetal development during the first 2 wk of gestation. Subsequently, maternal Cort might affect fetal development indirectly through regulating fetal adrenal function during the last week of gestation. Normally, fetuses are protected from any large excursions in maternal glucocorticoids by placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD-2), which inactivates cortisol and Cort (47). The expression and activity of 11β-HSD-2, however, are developmentally regulated and also subject to external influence. Thus fetal exposure to glucocorticoids represents net steroidogenic activity of the fetus itself plus a contribution of maternal glucocorticoids, subject to modulation by placental 11β-HSD-2. Maternal alcohol ingestion is also associated with elevated glucocorticoid levels and low birth weight in the fetus (13, 19, 49). In studies with rats, we have previously shown that, in response to maternal ethanol ingestion over the last 2 wk of gestation (beginning on day 8), maternal plasma Cort levels are consistently and significantly elevated from gestational day 18 to parturition (50). In contrast, fetal Cort levels are decreased (42, 65). Thus a highly significant inverse relationship between maternal and fetal glucocorticoid levels exists during the last week of gestation (42). An inverse relationship in the opposite direction exists between
Fetal and maternal Cort after maternal adrenalectomy (50) such that increased fetal Cort during the last week of gestation elevates maternal Cort levels to near normal by gestational day 21. However, alcohol exposure in adrenalectomized (Adx) dams still leads to significantly decreased fetal Cort levels in both sexes, suggesting that ethanol inhibits fetal Cort production directly. Because glucocorticoids in the fetus play a key role in the regulation of growth and maturation of many organ systems, as well as the programming of the postnatal hypothalamic-pituitary-adrenal axis itself, decreased fetal Cort levels, resulting from increased maternal Cort levels and/or ethanol, have the potential to permanently alter the physiology of the offspring.

We hypothesized that, if developmental exposure to high followed by low levels of fetal glucocorticoids are involved in cardiovascular vulnerability of the fetal alcohol-exposed (FAE) offspring, then maternal adrenalectomy, and the ensuing low levels of maternal Cort, would eliminate cardiovascular changes found in adult offspring. Therefore, the aim of the present study was to systematically measure in a rat model the effects of maternal ethanol consumption and maternal adrenalectomy on fetal body weight, placental weight, placental 11β-HSD-2 expression, and left ventricular weight in the adult. This information could suggest a potential mechanism of alcohol-induced fetal programming of the cardiovascular system.

METHODS

Animals. All animal procedures were approved by the Northwestern University Animal Care and Use Committee. Adult male and female Sprague-Dawley rats (viral free, 56-68 days of age; Harlan, Indianapolis, IN) were housed individually in a temperature- and humidity-controlled vivarium with regular light-dark cycles (lights on at 0700 and lights off at 1900). After 14 days acclimatization, rats were mated by placing a female in the male cage overnight. Mating was confirmed by microscopic analysis of vaginal smears for the presence of sperm the next morning. The day sperm was found was designated as gestational day 1.

Experiment 1a. Because low birth weight and increased placental weight are associated with prenatal exposure to increased glucocorticoids, this experiment aimed to measure plasma Cort levels of alcohol-consuming dams and fetal body weight and placental weight of their offspring. On gestational day 8, pregnant rats were randomly assigned to the following two experimental groups: FAE (n = 5) and pair fed (PF, n = 5). The FAE rats were placed on an ethanol-containing liquid diet (Lieber-DeCarli '82; BioServ) adjusted for pregnant rats containing 5% (wt/vol) ethanol (35% ethanol-derived calories), supplemented with essential minerals and vitamins. The ethanol diet was introduced in stages; 15% ethanol-derived calories was increased to 35% over 5 days, as described previously (50). The remaining rats were pair fed the same diet, with isocaloric substitution of cornstarch for the ethanol. The amount of ethanol-free diet given to rats in the PF group was based on the consumption of a corresponding dam of similar weight in the FAE group.

The liquid diets were started on gestational day 8 and were presented daily between 1600 and 1700, and daily intake was recorded. This amount of ethanol-diet consumption is not different from the alcohol intake of FAE dams reported previously, which produced blood ethanol levels of 80 mg/100 ml (39). On gestational day 21 the pregnant rats were killed by decapitation, and trunk blood was collected for Cort determination. Uterine horns were placed on ice, and fetuses were removed. The sex of each fetus was determined by anogenital distance, and then the fetus and placenta were weighed.

Experiment 1b. Low birth weight and increased placental weight (found in experiment 1a) are predisposing factors to cardiovascular vulnerability later in life. Thus we measured heart weight, specifically left ventricular weight, in adult FAE and PF offspring. The left ventricle was normalized to body weight, as it is most customary (9, 21, 23, 27, 28, 37, 60, 62, 70, 71) to control for the large sex differences in size. As in experiment 1a, pregnant rats were assigned to the same two treatment groups (PF, n = 5; FAE, n = 5). The diet administration protocol was identical, except that on gestational day 21 the diets were replaced with laboratory chow and water ad libitum, and the rats were allowed to deliver. Maternal daily alcohol consumption was similar to that in experiment 1a. Pups were weighed at 21 days of age and grouped by sex and treatment.

At 90–100 days of age, adult male and female rats from both prenatal treatment groups were killed by decapitation. Animals were weighed, hearts were removed and weighed, and then ventricles were separated and individually weighed.

Experiment 2a. If the cause of decreased body weight and increased placental weight is alcohol-induced elevated plasma Cort in the dam, this elevated maternal Cort needs to have access to the fetus via decreased protection by 11β-HSD-2. Thus removal of elevated maternal Cort in the alcohol-consuming dams by adrenalectomy could eliminate the increased placental weight and decreased 11β-HSD-2 expression. On gestational day 8, pregnant rats were randomly assigned to the following four experimental groups: FAE, adrenalectomized (Adx); PF, Adx; FAE, sham-adrenalectomized (Sham); and PF, Sham (n = 5).

Adrenalectomy was performed dorsally under anesthesia (n = 10, ketamine-xylazine, 87:10 mg/kg body wt), and the Sham dams (n = 10) underwent identical procedures without the removal of the glands. One-half of the Adx and Sham rats were placed on the FAE diet, which was introduced in stages, as described in experiment 1. The remaining Adx and Sham dams were placed on the PF diet. All Adx dams received their diet in 0.9% NaCl instead of water to prevent sodium depletion after adrenalectomy. To prevent resorption of the fetuses that occurs in Adx animals after surgery, a minimal replacement dose of Cort (2 µg/l; Sigma, St. Louis, MO) was included in the diet for 3 days after surgery, as described previously (50).

The liquid diets were started on gestational day 8 and were presented every day between 1600 and 1700; daily intake was recorded. Adrenalectomy did not alter alcohol metabolism, as shown in previous findings of identical blood alcohol levels in the Sham vs. Adx dams (90 ± 5.5 mg/100 ml; see Ref. 39). On gestational day 21 the pregnant rats were killed by decapitation. Fetal sex, weight, and placental weight were determined. Each placenta was frozen on dry ice and maintained at −80°C until extraction.

Experiment 2b. Because maternal adrenalectomy eliminated the increased placental weight and decreased 11β-HSD-2 expression in the female placenta in response to alcohol, we measured heart weight in the adult offspring of Adx dams to determine if the ventricular hypertrophy found in female offspring of alcohol-consuming mothers (experiment...
PCR using the following primer pairs: 5'-H11032 (17) using the Random Primers DNA Labeling System kit. The diet administration protocol was identical, except that on gestational day 21 the diets were replaced with laboratory chow and water ad libitum, and the rats were allowed to deliver. Maternal diet consumption was the same as that of the dams in experiment 2a. We have previously found no differences in body weight between the Sham and Adx adult offspring, so there was no need to cross-foster.

At 90–100 days of age, adult male and female rats from both prenatal treatment groups were killed by decapitation. Animals were weighed, hearts were removed and weighed, and then ventricles were separated and individually weighed.

RNA concentrations were measured as described previously (52) in unextracted plasma using 125I-labeled Cort.

RNA isolation and Northern analysis. Placental RNA was extracted using Trizol reagent, according to the manufacturer's protocol (Life Technologies, Grand Island, NY). The quality and quantity of RNA were analyzed by gel electrophoresis and spectrophotometry.

For Northern analysis, 8–10 μg RNA from each sample were separated by electrophoresis on a 1% agarose-formaldehyde gel, blotted on a nitrocellulose filter, and fixed by UV-cross-linking, as described previously (39). Filters were hybridized with cDNA probes overnight at 42°C in ULTRAhyb hybridization buffer (Ambion, Austin, TX) after prehybridization according to the manufacturer’s protocol. Probes were labeled with [32P]dCTP by random primer labeling protocol. Probes were provided by Dr. Michael Prystowsky, Albert Einstein University.

Table 1. Maternal body weight, total fetal and adult litter size, and average number of males and females

<table>
<thead>
<tr>
<th>Group</th>
<th>Maternal Weight, g</th>
<th>Total Fetal</th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Experiment 1a</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PF</td>
<td>389 ± 7.1</td>
<td>11.4 ± 1.1</td>
<td>4.8 ± 0.82</td>
<td>6.6 ± 1</td>
</tr>
<tr>
<td>FAE</td>
<td>307 ± 3.6*</td>
<td>9.2 ± 1.2</td>
<td>5 ± 0.8</td>
<td>4.2 ± 1.3</td>
</tr>
<tr>
<td><strong>Experiment 1b</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PF</td>
<td>385 ± 6.2</td>
<td>12.6 ± 0.67</td>
<td>6.7 ± 0.5</td>
<td>6 ± 0.62</td>
</tr>
<tr>
<td>FAE</td>
<td>311 ± 7.3*</td>
<td>8.84 ± 0.73*</td>
<td>5.1 ± 0.55</td>
<td>3.8 ± 0.67*</td>
</tr>
<tr>
<td><strong>Experiment 2a</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PF/SHAM</td>
<td>397 ± 5.2</td>
<td>14 ± 1.3</td>
<td>6 ± 0.8</td>
<td>7.9 ± 0.92</td>
</tr>
<tr>
<td>PF/ADX</td>
<td>392 ± 6.8</td>
<td>12.5 ± 1.4</td>
<td>7.7 ± 0.9</td>
<td>4.8 ± 0.1*</td>
</tr>
<tr>
<td>FAE/SHAM</td>
<td>318 ± 3.8*</td>
<td>13.7 ± 1.4</td>
<td>7.7 ± 0.9</td>
<td>6 ± 1</td>
</tr>
<tr>
<td>FAE/ADX</td>
<td>322 ± 4.4*</td>
<td>15.5 ± 1.7</td>
<td>8.5 ± 1.1</td>
<td>7 ± 1.2</td>
</tr>
<tr>
<td><strong>Experiment 2b</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PF/SHAM</td>
<td>390 ± 7.7</td>
<td>12 ± 0.81</td>
<td>6.3 ± 0.6</td>
<td>5.7 ± 0.74</td>
</tr>
<tr>
<td>PF/ADX</td>
<td>393 ± 6.5</td>
<td>13.2 ± 1.2</td>
<td>7 ± 0.91</td>
<td>6.3 ± 1.1</td>
</tr>
<tr>
<td>FAE/SHAM</td>
<td>316 ± 3.2*</td>
<td>9.4 ± 0.92*</td>
<td>5.9 ± 0.7</td>
<td>4.6 ± 0.84</td>
</tr>
<tr>
<td>FAE/ADX</td>
<td>318 ± 4.6*</td>
<td>8.3 ± 1.1*</td>
<td>4.3 ± 0.9*</td>
<td>5 ± 1.2</td>
</tr>
</tbody>
</table>

Values are means ± SE. There were five litters in the pair-fed (PF) and fetal-alcohol exposed (FAE) groups and five litters in the pair-fed/sham-adrenalectomized (PF/SHAM), fetal alcohol-exposed, sham-adrenalectomized (FAE/SHAM), pair-fed, adrenalectomized (PF/ADX), and fetal alcohol-exposed, adrenalectomized (FAE/ADX) treatment groups. *Significant difference from PF/Sham, **P < 0.01.

†Significant difference from PF/ADX, P < 0.05.
Fetal alcohol exposure led to left ventricular hypertrophy in the adult female FAE offspring. There was no effect of prenatal alcohol on body weight of adult offspring (data not shown) within the same sex. To avoid the sex difference in heart weight, the left ventricular weight was normalized to body weight. There was a significant increase [F(1,103) = 5.9; P < 0.05] in the left ventricular weight-to-body weight ratio in the adult FAE female compared with the PF female as seen in Fig. 2. Interestingly, no such difference was found in the male offspring. Left ventricular weight normalized to right ventricular weight revealed similar profiles (data not shown).

**Experiment 1a.** Although maternal Adx itself had no effect on fetal weight, the absence of maternal adrenal steroids potentiated the effect of alcohol in both females and males [diet × surgery F(1,347) = 28.4; P < 0.001; Fig. 3A]. Post hoc analysis revealed that both male and female FAE/Adx fetuses weighed significantly (P < 0.001) less than their respective PF/Adx controls, although only the female FAE/Sham fetuses were significantly (P < 0.01) smaller than the PF/Sham females. The FAE/Sham male fetuses tended (P = 0.08) to weigh less than the PF/Sham male fetuses.

There were differences between the fetal weights of Sham dams and those found in experiment 1a (Figs. 1A and 3A). These differences are likely because of the number of fetuses in each litter, since typically the larger the litter the less each individual fetus weighs. Also litter size tends to vary with the season (15), since dams tend to carry larger litters in the warmer months of the year. Experiment 1a was done in the winter, and the average litter size was smaller than in experiment 2a, which was carried out during the spring and summer.

Consistent with previous results from our laboratory (50), alcohol consumption significantly increased maternal plasma Cort levels [PF (n = 5): 97.5 ± 3.7 ng/ml; FAE (n = 5): 145.9 ± 7 ng/ml; (P < 0.01)] on gestational day 21.

Maternal ethanol consumption had significant impact on the size and physical development of the fetuses. Overall, both male and female fetuses in the FAE group were significantly [F(1,178) = 55.6; P < 0.001] smaller on gestational day 21 than those in the PF group (Fig. 1A). Furthermore, maternal ethanol ingestion also had a significant impact on the placenta (Fig. 1B). The placental weight of male and female FAE fetuses on gestational day 21 was significantly (P < 0.01) greater than that of PF fetuses.

**Experiment 1b.** As previously shown in our laboratory (52), plasma Cort levels were significantly (P < 0.05) decreased in FAE female (n = 8) offspring (31.2 ± 3.5 ng/ml) compared with PF female (n = 8) offspring (60.3 ± 6.6 ng/ml), although no such difference was found in the males.

decreased litter size was stillbirth or greater death rate of newborns in FAE litters.

**Fig. 1.** A: fetal weight on gestational day 21 (n = 26–34 males or females/diet). There were five litters in both the pair–fed (PF) and fetal-alcohol exposed (FAE) groups. Values are shown as means ± SE. *Significant difference from PF control, P < 0.001. B: placental weight on gestational day 21 for the animals described in A. Values are shown as means ± SE. *Significant difference from PF, P < 0.01.

Fetal alcohol exposure led to left ventricular hypertrophy in the adult female FAE offspring. There was no effect of prenatal alcohol on body weight of adult offspring (data not shown) within the same sex. To avoid the sex difference in heart weight, the left ventricular weight was normalized to body weight. There was a significant increase [F(1,103) = 5.9; P < 0.05] in the left ventricular weight-to-body weight ratio in the adult FAE female compared with the PF female as seen in Fig. 2. Interestingly, no such difference was found in the male offspring. Left ventricular weight normalized to right ventricular weight revealed similar profiles (data not shown).

**Experiment 2a.** Although maternal Adx itself had no effect on fetal weight, the absence of maternal adrenal steroids potentiated the effect of alcohol in both females and males [diet × surgery F(1,347) = 28.4; P < 0.001; Fig. 3A]. Post hoc analysis revealed that both male and female FAE/Adx fetuses weighed significantly (P < 0.001) less than their respective PF/Adx controls, although only the female FAE/Sham fetuses were significantly (P < 0.01) smaller than the PF/Sham females. The FAE/Sham male fetuses tended (P = 0.08) to weigh less than the PF/Sham male fetuses.

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mRNA levels in the female PF but not in the female FAE. Thus FAE females of Adx mothers had significantly \((P < 0.05)\) elevated 11\(\beta\)-HSD-2 mRNA levels compared with PF females of Adx mothers.

**Experiment 2b.** There were no differences in plasma Cort levels among the Adx offspring \((n = 8 \text{ rats/group})\). However, as previously found in our laboratory \((52)\), basal Cort levels were decreased significantly \((P < 0.05)\) in FAE/Sham females \((32.3 \pm 6.75 \text{ ng/ml})\) compared with PF/Sham females \((56.59 \pm 6.4 \text{ ng/ml})\), whereas no differences were found in the Sham males. These findings are similar to those found in the adult offspring from experiment 1b.

Although left ventricular hypertrophy was confirmed in the adult female offspring after prenatal alcohol exposure, this effect of ethanol on the left ventricular weight-to-body weight ratio (Fig. 5) was abolished by maternal adrenalectomy \([\text{sex} \times \text{diet} \times \text{surgery}, F(1,238) = 15.8; P < 0.001]\). Post hoc analysis revealed a significant \((P < 0.05)\) increase in the ratio of left ventricular weigh to body weight in female FAE/Sham offspring compared with PF/Sham adult females similar to those shown in Fig. 2, but no such increase was found between the female Adx groups. No differences were found in left ventricular weight-to-body weight ratio in the adult male offspring of experimental dams. As found in experiment 1b, there were no differences in body weight among the treatment groups, only the typical sex difference, and left ventricular weight normalized to right ventricular weight showed profiles similar to those of Fig. 5 (data not shown).

**DISCUSSION**

The main findings of the present study suggest that maternal adrenal hormones might contribute to the cardiovascular changes found in adult female offspring.
exposed to ethanol in utero. In the present study, maternal ethanol ingestion produced hypertrophy of the left ventricle in the adult FAE female offspring, which was normalized by maternal adrenalectomy. Maternal adrenalectomy also normalized the increased placental weight found in fetuses of both sexes in response to FAE.

The mRNA levels of placental 11β-HSD-2 mRNA, which control the amount of Cort exposure to the fetus, were increased in the FAE male but decreased in female placenta on gestational day 21. Maternal adrenalectomy eliminated the increased 11β-HSD-2 mRNA levels in the FAE males while in the FAE females 11β-HSD-2 expression was increased significantly compared with PF females after maternal Adx. Therefore, one likely explanation for the left ventricular hypertrophy found in the adult female FAE offspring is exposure to increased maternal steroids secondary to the decreased levels of placental 11β-HSD-2 mRNA.

Increasing evidence associates events occurring early in life with permanent impact (47). For example, low birth weight and increased placental size strongly predict the subsequent occurrence of hypertension, insulin resistance, and ischemic heart disease deaths in adulthood (3, 6, 7, 46, 69). However, there is evidence for vulnerability to cardiovascular abnormalities, such as left ventricular hypertrophy, in the absence of hypertension (45). In these respects, our FAE animal model exhibits a pattern similar to these models of fetal origins of adult disease. The present study also confirmed previous findings of increased placental weight (18, 20) and low birth weight (1, 25, 26) of FAE offspring. It is of interest that this lower weight in the FAE fetus coupled with a lower body weight of the FAE dam occurred despite the similar caloric consumption of FAE and PF dams. Thus this decreased body weight of the FAE mother and fetus may be because of increased metabolic rate in the alcohol-consuming dam or the less than perfect pair-feeding paradigm used by us and many other laboratories.

Cardiac malformations exist in children with fetal alcohol syndrome (44, 53) and animal models of prenatal alcohol exposure (43, 57), and cardiac hypertrophy has been found in children with fetal alcohol syndrome (68). Prenatal ethanol exposure has been shown to cause ultrastructural abnormalities in cardiac muscle cells in mice (63) and a significant difference in left ventricular muscle width in male rats (41). The high incidence of heart defects indicates that alcoholism during pregnancy has to be considered as a serious and preventable cause of congenital heart disease.

In humans and laboratory animals, prenatal glucocorticoid administration is associated with low birth weight, increased placental weight, cardiovascular disease, and potentially permanent hypertension (11). Excess glucocorticoid exposure in utero retards fetal growth in both humans and animals (32, 34, 40, 46), and cortisol affects placental size (22). Therefore, fetal overexposure to endogenous glucocorticoids (because of prenatal stress, prenatal alcohol, or reduced activity of placental 11β-HSD-2) may represent a common link between the prenatal environment, fetal growth, and adult disorders (66). However, the mechanisms by which excessive maternal glucocorticoids exert these effects is not known.

Placental 11β-HSD-2 serves as the barrier to protect the fetus from excess maternal glucocorticoids. Its activity correlates with birth weight (47), and inhibition of placental 11β-HSD-2 in rats decreases birth weight (48). Our data demonstrated that prenatal alcohol exposure affects 11β-HSD-2 mRNA levels in a sexually dimorphic manner: decreasing in females and increasing in males. 11β-HSD-2 mRNA levels are shown to correlate with enzyme activity (54, 55). Because testosterone can potentially downregulate 11β-HSD activity, as has been found to occur in rat testis (35), placental 11β-HSD-2 can be higher in females than in males. However, testosterone levels are decreased in the male FAE fetus (2, 50) in correspondence with the increased levels of 11β-HSD-2 mRNA found in the male FAE placenta. This increase in 11β-HSD-2 mRNA could additionally be attributable to the lower levels of estradiol via the aromatization of decreased testosterone levels in the FAE male fetus. Placental estrogen is the product of the aromatase cytochrome P-450 enzyme that uses androgens as substrates (8), and estrogens inhibit placental 11β-HSD-2 activity (52). The increased levels of 11β-HSD-2 mRNA found in the FAE male placenta might protect the fetus, and subsequently the adult offspring, from left ventricular hypertrophy later in life. In contrast, estradiol is increased in the female FAE fetus compared with PF control (2), and these increased levels of estrogen could lead to increased estrogen-induced inhibition of 11β-HSD-2 expression. Subsequently, the decreased levels of 11β-HSD-2 may lead to left ventricular hypertrophy in the adult female FAE offspring, since 11β-HSD-2 has an important role in regulating fetal growth and

![Graph](image-url)
the subsequent development of cardiovascular disease in adulthood (31).

Previous studies have indicated that adult females are more susceptible than males to some of the effects of prenatal alcohol (29, 33, 58, 59, 64). Our study appears to follow the same sexually dimorphic pattern. Adult female FAE rats demonstrated left ventricular hypertrophy in this study, and this hypertrophy was abolished by maternal adrenalectomy. Although placental 11β-HSD-2 mRNA levels were decreased in the females on gestational day 21 in response to maternal ethanol ingestion, the combination of maternal adrenalectomy and prenatal alcohol increased placental 11β-HSD-2 expression compared with those of the PF/Adx females. Placental 11β-HSD-2 activity is regulated by fetal cortisol levels in an inhibitory fashion in sheep (12). Our laboratory has previously shown that maternal Adx resulted in compensatory increases in fetal Cort levels that were attenuated in fetuses of Adx dams on alcohol (50). Accordingly, the lower placental 11β-HSD-2 mRNA levels in the PF/Adx females, compared with those of PF/Sham, and the higher levels in the female FAE/Adx placenta may reflect the effect of these differences in fetal Cort levels on this placental enzyme. In Adx dams, alcohol cannot elevate maternal Cort levels, but plasma Cort levels of fetal origin still rise in FAE and PF Adx dams equally by gestational day 21 (50). However, the levels of maternal Cort in the Adx dams are still significantly lower than in Sham dams. Thus the lower maternal Cort in the Adx dams together with the higher placental 11β-HSD-2 expression in the female FAE placenta appear to protect the female FAE fetus and may indeed be the cause of the elimination of left ventricular hypertrophy in the adult FAE female offspring of Adx dams consuming alcohol.

The present findings suggest that the FAE-induced changes in placental 11β-HSD-2 mRNA levels and left ventricular heart weight are coupled in the female offspring and depend on maternal adrenal status. In contrast, increased placental 11β-HSD-2 levels in FAE males may protect the male fetus from subsequent ventricular hypertrophy. These experiments support the hypothesis that adaptations to the fetal environment, which result in low birth weight, also “program” physiological changes in the adult.

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