Hypertension Research (2022) 45:1835–1837
https://doi.org/10.1038/s41440-022-01021-z

COMMENT

Effect of estrogen on fetal programming in offspring from high-fat-fed mothers

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Keywords Maternal high-fat diet · Vascular dysfunction · Estrogen · Fetal programming · Offspring

Received: 13 August 2022 / Accepted: 16 August 2022 / Published online: 14 September 2022

Sex differences in the renin-angiotensin system (RAS) have been widely investigated [1]. Generally, premenopausal females have been shown to be protected from cardiovascular disease through regulation of the RAS by estrogen using ovariectomized (OVX) animals. Ovariectomy in the female rat is associated with an increase in the expression of the angiotensin (Ang) II type 1 (AT_1) receptor in the heart, kidney, lung, abdominal aorta, adrenal gland, and cardiovascular regulatory nuclei in the brain [2]. We have also reported sex-specific protective effects of the Ang II type 2 (AT_2) receptor on vascular remodeling, brain injury, and cognitive function using OVX female mice [3–5]. 17β-Estradiol (E_2) replacement diminished the changes in RAS components observed in OVX rodents.

On the other hand, the influence of the fetal environment on cardiovascular development has been recently highlighted. In particular, maladaptation between the intrauterine and external environments induced by fetal growth restriction (FGR) was shown to be associated with dysregulation of the RAS in basic studies [6]. We previously reported that AT_2 receptor signaling is involved in cardiovascular disorders of adult offspring with FGR [7]. Moreover, the Ang II concentration in FGR offspring was markedly elevated compared with that in controls in a clinical study performed approximately thirty years ago [8].

The current paper in Hypertension Research by Chen et al. demonstrated that vasoconstriction by Ang II treatment was only observed in OVX female offspring from high-fat diet (HFD)-loaded dams via increased expression of the AT_1 receptor and a lack of change in the AT_2 receptor [9]. They also showed that maternal HFD significantly decreased the methylation level of the AT_1 receptor but not the AT_2 receptor. E_2 replacement prevented such Ang II-induced vasoconstriction with reversion of AT_1 receptor expression (Fig. 1). Additionally, Chen et al. previously reported in Hypertension Research that maternal HFD increased phenylephrine- and Ang II-induced contractions of the aorta in male but not female offspring, using almost the same protocol as the present study [10]. In male rats, the AT_1 receptor was increased and the AT_2 receptor was decreased with changes in the DNA methylation of each receptor promotor, while both receptors were increased in female rats (Fig. 1). The present study is a further investigation of their previous work, focusing on female rats. They also reported that maternal HFD causes the development of cardiac hypertrophy in OVX female offspring [11]. E_2 replacement attenuated cardiac hypertrophy by regulating the AT_2 receptor. Interestingly, maternal HFD decreased glucocorticoid receptor binding to glucocorticoid response elements at the AT_2 receptor promoter. E_2 replacement diminished such binding; thus, both AT_1 and AT_2 receptors play a crucial role in reflecting the fetal environment in offspring dependent on the organs, and estrogen has a protective role in cardiovascular maladaptation by regulating the expression of such angiotensin II receptors.

However, several questions exist in relation to the present study. Maternal HFD has been widely used as a maternal obesity model. Fetal weight depends on the fat ratio [12]. Similar to the present study, a 60% fat diet fed for 4-9 weeks prior to pregnancy tended to increase fetal growth, whereas feeding 60% fat for a longer period tended to reduce fetal growth. In these studies by Chen et al., HFD was fed from Day 1 to Day 21 of gestation according to their previous studies, and the body weight of the offspring on postnatal Day 7 was lower than that with

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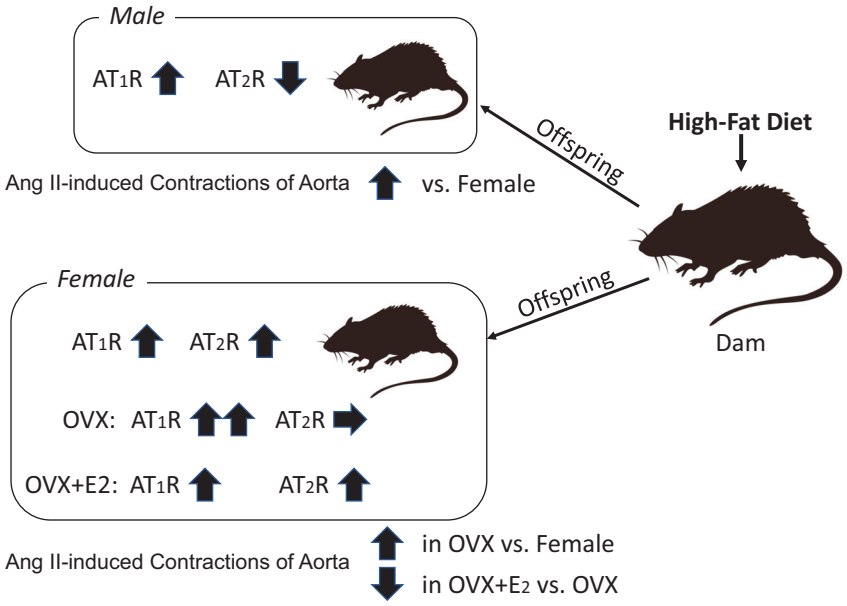

Fig. 1 Schematic presentation of the sex differences in angiotensin II receptor expression and angiotensin II-induced contractions of the aorta in offspring from high-fat diet-fed dams. Ang II; angiotensin II, AT_1R; angiotensin II type 1 receptor, AT_2R; angiotensin II type 2 receptor, OVX; ovariectomy, E_2; estrogen treatment

a control diet, indicating that this protocol induces fetal growth restriction. However, it is difficult to understand the study design in which maternal HFD treatment was limited to after pregnancy. Moreover, in Figure 4, even though the mRNA level of the AT_2 receptor was not altered in the three groups fed a HFD, the protein expression of the AT_2 receptor was increased in HFD-sham and HFD-OVX with E_2 replacement offspring. Moreover, the effect of E_2 replacement on the CpG methylation of the AT_1 and AT_2 receptors is not shown in Figure 5. Thus, the actual effect of estrogen on AT_2 receptor regulation should be investigated in the future.

Recently, the effects of the protective arms of the RAS, such as the Ang (1-7)-angiotensin-converting enzyme 2 (ACE2)-Mas receptor axis, have been highlighted. Sex differences in cardiovascular actions focusing on such protective arms involving the association with estrogen have been reported [13, 14]. Recently, Fernandes et al. demonstrated that Ang (1-7) and des-Arg^{9}BK metabolites are novel biomarkers of childhood obesity [15]. Nozato and Yamamoto commented on this article with a thematic presentation of a proposed hypothesis of the association between fetal programming and the Ang (1-7)-ACE2-Mas receptor axis in the development of childhood obesity [16]. Thus, future progression of this model focusing on such a new axis is expected.

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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