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Sex differences in the developmental programming of hypertension

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Abstract

Experimental models of developmental programming provide proof of concept and support Barker's original findings that link birth weight and blood pressure. Many experimental models of developmental insult demonstrate a sex difference with male offspring exhibiting a higher blood pressure in young adulthood relative to their age-matched female counterparts. It is well recognized that men exhibit a higher blood pressure relative to age-matched women prior to menopause. Yet, whether this sex difference is noted in individuals born with low birth weight is not clear. Sex differences in the developmental programming of blood pressure may originate from innate sex-specific differences in expression of the renin angiotensin system that occur in response to adverse influences during early life. Sex differences in the developmental programming of blood pressure may also involve the influence of the hormonal milieu on regulatory systems key to the long term control of blood pressure such as the renin angiotensin system in adulthood. In addition, the sex difference in blood pressure in offspring exposed to a developmental insult may involve innate sex differences in oxidative status or the endothelin system, or may be influenced by age-dependent changes in the developmental programming of cardiovascular risk factors such as adiposity. Therefore, this review will highlight findings from different experimental models to provide the current state of knowledge related to the mechanisms that contribute to the etiology of sex differences in the developmental programming of blood pressure and hypertension.

Keywords

Sex hormones; renin angiotensin system; oxidative stress; endothelin; renal nerves; blood pressure

The theory of the developmental origins of programmed hypertension and cardiovascular (CV) disease proposes that adverse events during early life can impact blood pressure and

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CONFLICT OF INTEREST

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CV health in later life (Tarry-Adkins and Ozanne, 2011). The first epidemiological study linking early life events with long-term consequences on blood pressure and CV function were reported by Forsdahl in the 1970s (Forsdahl, 1977). This study complemented later studies by Barker in the 1980s who narrowed the importance of early life influences on later blood pressure and CV health to the fetal period (Barker et al., 1989). Epidemiological studies indicate that an inverse relationship between birth weight and blood pressure is observed at all stages of life including children, young adulthood and the elderly (Barker and Osmond, 1988). Proof of concept for this association is supported by an extensive number of experimental models as described by Nathanielsz in his review on animal models and the developmental origins of adult diseases (Nathanielsz, 2006). Despite the method or timing of developmental insult, different experimental models exhibit a sex difference in adult blood pressure following an adverse perinatal event (Alexander 2003; Katkhuda et al. 2012; Moritz et al. 2009; Tao et al. 2013; Woods et al. 2001, 2005; Xiao et al. 2008). Yet, whether a sex difference in the inverse relationship between birth weight and blood pressure is observed in the human population is unclear (Richardson et al. 2011; Gamborg et al. 2007; Lawlor et al. 2002). Furthermore, the exact mechanism(s) that contribute to the sex difference in adult blood pressure following an insult during early life have not yet been fully elucidated. Inherent sex differences in the response to a developmental insult may originate during fetal life and contribute to the sexual dimorphism in blood pressure in adulthood (Woods et al. 2001, 2005). After puberty sex hormones may modulate factors involved in the long-term control of blood pressure. Testosterone may play a permissive role (Ojeda et al. 2007b) whereas estrogen may be protective (Ojeda et al. 2007a) via modulation of the renin angiotensin system (**RAS**). Innate sex differences in oxidative stress (Ojeda et al. 2012) or endothelin (Bourgue et al. 2013) may also play a role. In addition, the development of age-dependent cardiovascular risk factors such as adiposity (Intapad et al. 2013) may also contribute to the sexual dimorphism of blood pressure (Intapad et al. 2013) programmed by a developmental insult.

Within the general population experimental and epidemiological studies indicate a sex difference in blood pressure that is higher in males compared to females (Sandberg and Ji, 2012). Blood pressure is inversely related to birth weight in both men and women (Jarvelin et al. 2004; Curhan et al. 1996a, 1996b); yet, several studies suggest that the degree of programmed insult may be greater in men versus women in a manner that is age-dependent (Jones et al. 2008; Hallan et al. 2008; Andersson et al. 2000). Sex differences are observed in experimental studies with blood pressure more severely compromised in males than females in young adulthood in models that utilize dietary manipulation during early life (Woods et al. 2005), placental insufficiency (Ojeda et al. 2007a; Ojeda et al. 2007b) and maternal diabetes (Katkhuda et al. 2012) or with age in models induced by prenatal exposure to nicotine (Tao et al. 2013) to induce a developmental insult. In addition, enhanced blood pressure sensitivity to vasoactive factors such as angiotensin II (Ang II) is greater in male offspring relative to female offspring exposed to nicotine during fetal life (Xiao et al. 2008) or early life stress (Loria et al. 2013) implicating that impaired regulation of blood pressure control originates from an insult in early life in a manner that is sex-specific. This review will provide an overview of the potential mechanisms that contribute to the sex difference in the developmental programming of blood pressure.

Nephron number and blood pressure

The kidneys play a critical role in fluid and electrolyte homeostasis and blood pressure regulation (Guyton et al. 1972). Low birth weight (LBW), or a birth weight of 2500g or less, serves as a crude marker for slow fetal growth and LBW infants exhibit a reduction in nephron number relative to normal birth weight counterparts (Hotoura et al. 2005; Basioti et al. 2009; Baum 2010). A reduction in nephron number is also closely linked to hypertension (Brenner et al. 1988; Zandi-Nejad et al. 2006). Based on this association, Brenner proposed that a congenital reduction in nephron number may contribute to hypertension in later life (Brenner et al. 1988). A reduction in nephron number is also a common observation noted in many different experimental models of developmental insult including those induced via prenatal exposure to maternal dexamethasone (Wlodek et al. 2008) or undernutrition (Woods et al. 2001; Gilbert et al. 2007). In addition, a reduction in nephron number is observed in experimental models that utilize the rat or sheep (Gilbert et al. 2007; Mitchell et al. 2004) suggesting that developmental insults program a reduction in nephron number in a manner that is not species specific. Yet, a reduction in nephron number may (Woods et al. 2005) or may not (Moritz et al. 2009) be associated with the developmental programming of hypertension. Fetal exposure to moderate maternal protein restriction programs a reduction in nephron number associated with hypertension in the male (Woods et al., 2001), but not the female rat relative to the same-sex control counterpart (Woods et al. 2005). However, uteroplacental insufficiency programs a comparable nephron deficit in growth-restricted male and female rats with hypertension observed only in the male offspring relative to male control or the female (Moritz et al. 2009). Induction of a congenital deficiency in nephron number via fetal nephrectomy (uni-x) is associated with the development of hypertension in the male uni-x sheep relative to male control; yet, the development of hypertension is delayed in the female uni-x counterpart in a manner that is estrogen dependent (Singh et al. 2010). Thus, these studies suggest that female offspring exposed to an adverse event in early life may be protected against the development of programmed hypertension despite a similar deficit in nephron number. Furthermore, these studies indicate that other mechanisms beyond a deficient in nephron number per se contribute to the sex-specific programming of hypertension following a developmental insult.

Sex hormones and blood pressure

The male spontaneously hypertensive rat (SHR) has a higher blood pressure relative to the age-matched female SHR at 4 to 5 months of age (Reckelhoff et al. 2000). Castration reduces blood pressure in the male SHR to levels comparable to the age-matched female SHR suggesting that testosterone plays a permissive role in the etiology of sex differences in blood pressure regulation in the young SHR. The importance of testosterone in mediating sex differences in blood pressure programmed in response to a developmental insult is also noted in the model of intrauterine growth restriction (IUGR) induced via placental insufficiency (Ojeda et al. 2007b). Circulating levels of testosterone are elevated two-fold in male growth-restricted offspring relative to male control (Ojeda et al. 2007b). Hypertension in adult male growth-restricted offspring is abolished by castration (Ojeda et al. 2007b) indicating that hypertension in this model of developmental insult is testosterone dependent. Yet, castration fails to abolish hypertension in male offspring exposed to maternal protein

restriction during fetal life (Woods et al. 2010). However, this finding is not unexpected since circulating testosterone levels do not differ in male low protein offspring relative to their male control counterparts (Woods et al. 2010). Thus these data suggest that the sex-specific mechanisms that program hypertension in response to different models of undernutrition during fetal life may be insult specific.

Not all models of developmental insult exhibit overt hypertension. Maternal separation during lactation in the rat is a model of early life stress that programs heightened angiotensin II (Ang II)-dependent hypertension (Loria et al. 2010). Castration abolishes the enhanced blood pressure response to chronic Ang II in male offspring exposed to early life stress relative to their male control counterparts (Loria et al. 2013) implicating an important role for testosterone in mediating the programming of increased CV risk in this model.

Castration also abolishes the enhanced blood pressure response to acute Ang II in male growth restricted offspring exposed placental insufficiency (Ojeda et al. 2010). Thus, these studies also indicate testosterone as a permissive factor in the developmental programming of enhanced blood pressure sensitivity to Ang II despite the method, early life stress (Loira et al. 2013) or placental insufficiency (Ojeda et al. 2010), or the timing, prenatal (Ojeda et al. 2010) versus post-natal (Loria et al. 2013), of the developmental insult

Sex differences in the developmental programming of blood pressure are not limited to the influence of testosterone. Female growth-restricted rats exposed to placental insufficiency are normotensive in young adulthood (Alexander 2003). Although hypertension in their male growth-restricted counterparts is testosterone dependent (Ojeda et al. 2007b), estrogen may also contribute to the sexual dichotomy of blood pressure in this model. Ovariectomy has no significant impact on blood pressure in female control offspring; however, ovariectomy induces hypertension in female growth-restricted offspring relative to female control, intact or ovariectomized (Ojeda et al. 2007a). In addition, estrogen replacement restores blood pressure in ovariectomized female growth-restricted offspring to levels comparable to their female control counterparts (Ojeda et al. 2007a) suggesting a protective role for estrogen against the adverse impact of a developmental insult. Removal of the ovarian hormones via ovariectomy also enhances sensitivity to acute Ang II in female growth-restricted offspring in this model of developmental insult (Ojeda et al. 2011). Ovariectomy also induces an enhanced sensitivity to acute Ang II in young adult female rat offspring exposed to nicotine during fetal life relative to female control; an effect that is reversed by estradiol replacement (Xiao et al. 2013). Thus, these studies suggest that estrogen is protective against the developmental programming of blood pressure in the young adult female and may also contribute to the sex difference in the developmental programming of blood pressure in young adulthood. Yet, the importance of estrogen in other models of developmental insult has not yet been tested and requires further investigation.

Sex specific programming of the renin angiotensin system

Angiotensin II acting through its angiotensin type 1 receptor (AT₁R) is necessary for normal renal development (Tufro-McReddie et al. 1995). Studies from the laboratories of Woods and Salazar demonstrate that perinatal blockade of the AT₁R in the rat is associated with a decrease in nephron number (Woods and Rasch 1998; Saez et al. 2007). Moreover, blood

pressure is increased in rat offspring exposed to perinatal blockade of the AT₁R (Woods and Rasch 1998, Saez et al. 2007) indicating that the suppression of the RAS during renal development is associated with a long-term effect on blood pressure regulation. Intrarenal renin and Ang II protein expression are reduced in rat offspring of nutrient restricted dams that exhibit a reduction in nephron number associated with an increase in blood pressure relative to offspring of control dams (Woods et al. 2005). Suppression of intrarenal renin expression is also observed in male growth-restricted rats that exhibit a marked increase in blood pressure in adult life programmed in response to placental insufficiency (Grigore et al. 2007). Thus, suppression of the RAS may be one mechanism by which the fetal environment programs an increase in blood pressure. Yet, innate sex differences in expression of the intrarenal RAS are observed in response to an adverse fetal insult. Whereas hypertensive male rat offspring of protein restricted dams exhibit suppression of intrarenal renin expression and Ang II production during development (Woods et al. 2001), expression of intrarenal renin and Ang II production during fetal life is maintained in female low protein rats (relative to control counterparts) that remain normotensive in adulthood (Woods et al. 2005). Thus, these studies suggest that sex differences in adult blood pressure programmed in response to a fetal insult may result from the innate sex-specific programming of the RAS during nephrogenesis (for a comprehensive review, see Moritz et al. 2010). Additionally, these studies indicate that the protective effect of the female sex against developmental programming of hypertension in young adulthood may have its origins during fetal life. Importantly, the impact of sex on the intrarenal RAS extends into adulthood with regulation of the RAS via sex steroids serving as another contributory factor in the sex-specific developmental programming of hypertension.

The renin angiotensin system (RAS) is a systemic hormonal regulator of sodium reabsorption, vasoconstriction, aldosterone production and vasopressin secretion with direct effects on blood pressure regulation. The RAS exhibits autocrine and paracrine capabilities in numerous organs including the kidneys, placenta and the brain (Moritz et al. 2010). The regulatory effect of the RAS is exerted by a balance between its vasoconstrictor and vasodilator pathways (Fyhrquist and Saijonmaa 2008). Sex hormones differentially regulate the vasoconstrictor and vasodilator pathways of the RAS by increasing or decreasing circulating and tissue-specific RAS and impacting the long-term regulation of water and electrolyte homeostasis and blood pressure (Fischer et al. 2002; Hilliard et al. 2013). Blockade of the RAS abolishes hypertension in adult growth-restricted rats exposed to placental insufficiency (Ojeda et al. 2010) or maternal protein restriction during fetal life (Manning and Vehaskari 2001) implicating the RAS as a potential contributor to the etiology of programmed hypertension despite the method of developmental insult. The exact contribution of the RAS to the etiology of hypertension programmed by fetal exposure to a developmental insult is not clear; yet, modulation of the RAS via sex hormones may contribute to sex differences in blood pressure in different models of developmental insult.

Renal expression of renal renin and angiotensinogen are androgen dependent in the male SHR (Chen et al. 1992) suggesting hypertension in this model may involve androgen-induced activation of the RAS. Hypertension programmed by exposure to placental insufficiency in the rat is associated with an increase in circulating testosterone and significant increases in renal renin, angiotensin, and ACE expression in male growth-

restricted rats (Grigore et al. 2007). Despite up-regulation of intrarenal renin, Ang II and ACE (Grigore et al. 2007) and attenuation of hypertension by blockade of the RAS in this model (Ojeda et al. 2007b), renal Ang II or renal AT1R expression are not increased in the hypertensive male growth-restricted rat (Grigore et al. 2007). Thus, the exact mechanism by which the RAS contributes to the etiology of IUGR-induced hypertension is not clear. Renal ACE expression is not elevated in female growth-restricted counterparts that are normotensive in adulthood (Ojeda et al. 2007a). Yet, expression of renal ACE2, a component of the vasodilator arm of the renal RAS, is increased in female growth-restricted rats relative to their female control counterparts (Ojeda et al. 2007a). The increase in renal ACE2 expression in female growth-restricted rats is abolished by ovariectomy implicating a role for the ovarian hormones in the control of its expression (Ojeda et al. 2007a). Whether changes in intrarenal ACE2 translate into alterations in expression of Ang-(1-7) has not yet been determined; however, this study suggests that up-regulation of compensatory pathways of the RAS in the female rat exposed to a developmental insult is ovarian hormone dependent. Other models of developmental insult exhibit sex specific programming of the intrarenal RAS (for a comprehensive review, see Moritz et al. 2010) although the direct importance of sex and the RAS has not been fully tested. Clearly further investigation is needed to adequately address the importance of the RAS, the exact contribution of sex, and how differential regulation of the RAS by the hormonal milieu contributes to sex differences in blood pressure programmed in response to a developmental insult.

To conclude, the impact of sex on the intrarenal RAS originates during fetal life and persists into adulthood. Sex-dependent changes in the intrarenal RAS during fetal life and adulthood are associated with the developmental programming of hypertension suggesting that sex-specific programming of the intrarenal RAS may contribute to the developmental programming of hypertension. The direct impact of sex-specific changes in the RAS in the developmental programming of hypertension is not clear. Therefore, additional studies are warranted to clarify how differential programming of the RAS in male and female offspring contributes to sex-specific programming of blood pressure following an insult during early life.

Sex specific regulation of oxidative stress

Intrauterine development involves a delicate balance between reactive oxygen species (ROS) and antioxidant mechanisms. The cellular generation of ROS is associated with the progression of placentation and involves switching of a cellular reduced redox state to an oxidized state to initiate cellular differentiation (Hitchler and Domann 2007). However, the fetal environment is low in oxygen and sensitive to oxidative injury because of its low antioxidant capacity (Dennery 2010). An increase in oxidative stress that occurs in response to placental hypoxia in pregnancies complicated by preeclampsia contributes to the development of low birth weight (Peuchant et al. 2004; Roberts and Lain 2002). Pregnancies complicated by maternal diabetes also demonstrate enhanced oxidative stress (Gauster et al. 2012). Fetal exposure to adverse levels of oxidative stress during development can induce genetic and epigenetic alterations that may result in long-term consequences for the fetus (Cerdeira and Weitzman 1997). Markers of oxidative stress are elevated in cord blood from the male relative to the female fetus following preterm delivery (Minghetti et al. 2013; Stewart

et al. 2005). Thus, innate sex differences in oxidative stress may initiate during fetal life. However, sex differences in oxidant stress may contribute to the sex specific developmental programming of hypertension in later life.

Markers of oxidative stress are increased in children born small for gestational age in a manner linked to systolic blood pressure (Chiavaroli et al. 2009). Plasma levels of Ang II and plasma ACE activity are also elevated in low birth weight children (Franco et al. 2008). Regulation of blood pressure via Ang II involves the generation of ROS (Mehta and Griending 2007) and an increase in oxidative stress contributes to the enhanced vascular sensitivity to acute Ang II induced by prenatal exposure to nicotine (Xiao et al. 2011). Oxidative stress also contributes to the etiology of hypertension programmed by fetal exposure to undernutrition and placental insufficiency (Franco Mdo et al. 2002; Katkhuda et al. 2012; Ojeda et al. 2012; Stewart et al. 2005). Recent studies implicate a sex-specific role for oxidative stress in the developmental programming of hypertension. Hypertension in male growth-restricted rats exposed to a developmental insult such as placental insufficiency (Ojeda et al. 2012) or male rats exposed to maternal diabetes (Katkhuda et al. 2012) is associated with a marked increase in renal markers of oxidative stress relative to the normotensive male control counterpart. Yet, no change in oxidative status is observed in normotensive female growth-restricted rats relative to their female control counterparts in these models (Katkhuda et al. 2012; Ojeda et al. 2012). A marked increase in renal antioxidants is observed in normotensive female growth-restricted rats relative to their female control counterparts in the model of insult programmed by placental insufficiency (Ojeda et al. 2012). Thus, innate sex differences in oxidative stress may contribute to the sex-specific developmental programming of hypertension with up-regulation of compensatory antioxidants in the female serving a potential mediator against the increase in oxidative stress. However, additional studies are needed to clarify if innate sex differences in oxidative status are crucial mediators of sex-specific programming of hypertension in response to an adverse event in early life.

Sex specific programming of the endothelin system

Sex differences in the developmental programming of hypertension involve innate sex-specific programming of the RAS and oxidative stress. Other potential factors may also contribute although to date, few studies have provided in-depth investigation into their relative importance. Endothelin is a potent vasoconstrictor implicated in the etiology of hypertension via the vasoconstrictor actions of the endothelin type A (ETA) receptor (Speed and Pollock 2013). Renal endothelin-1 mRNA levels are higher in male relative to female rats; castration reduces this innate sex difference (Montezano et al. 2005). However, ovariectomy is associated with an increase in endothelin-1 mRNA expression in the female rat and this increase is reversed by estrogen (David et al. 2001). Males also exhibit an enhanced ETA receptor mediated responses (see Kittikulsuth et al. for an in-depth review on sex differences in the renal actions of endothelin, (Kittikulsuth et al. 2013). Thus, these studies implicate a role for sex hormones in the modulation of the endothelin system. Prenatal hypoxia programs hypertension in aged (14 months) male, but not aged female IUGR offspring relative to their same-sex control counterpart (Bourque et al. 2013). Blockade of the endothelin type A (ETA) receptor, or the receptor that mediates the

vasoconstrictor actions of endothelin, reduces blood pressure to a greater extent in male IUGR relative to male control rats indicating endothelin may contribute to hypertension induced via prenatal hypoxia in the male IUGR rat (Bourque et al. 2013). Blockade of the ETA receptor has no significant effect on blood pressure in female rat offspring exposed to prenatal hypoxia (Bourque et al. 2013) further implicating a role for endothelin as a potential mediator of the sex-specific programming of hypertension in this model of developmental insult. The endothelin system is implicated in contributing to the enhanced pressor response to air jet stress in male rats exposed to early life stress (Loria et al. 2010). Development of Ang II-dependent hypertension is delayed in female rats exposed to early life stress relative to their male counterparts (Loria et al. 2013). Endothelin plays a role in Ang II hypertension (Alexander et al. 2001) and female rats in general are not as susceptible to Ang II hypertension as males (Reckelhoff et al. 2000). Whether endothelin plays a role in mediating sex differences in the development of Ang II hypertension in this model of developmental insult induced by early life stress is not yet known. However, these studies indicate that endothelin as an important mediator of sex-specific programming of blood pressure requires more investigation.

Increased susceptibility to hypertension in later life

Models of undernutrition during fetal life program dysregulation of energy balance resulting in obesity in later life (Lukaszewski et al. 2013). Female growth-restricted offspring in the model of placental insufficiency induced by a reduction in uterine perfusion in the rat are normotensive in young adulthood (Alexander, 2003); yet exhibit overt hypertension relative to age-matched female control offspring by one year of age in association with an increase in adiposity (Intapad et al. 2013). Thus, this study indicates that protection against the adverse impact of a developmental insult on later blood pressure regulation in the female exposed to a developmental insult may be lost with age. In addition, this study indicates that an age-dependent increase in adiposity may be a contributory factor in the development of age-dependent hypertension in the female growth-restricted rat. Whether this age-dependent increase in blood pressure in the female growth-restricted rat involves changes in the hormonal milieu is not yet known, but estrogen is demonstrated to serve as a protective factor against the developmental programming of hypertension in young adulthood in this model of development insult (Ojeda et al. 2007a).

Female growth-restricted offspring in a model of placental insufficiency induced via bilateral uterine ligation do not exhibit a marked increase in blood pressure relative to female control by 18 months of age (Moritz et al. 2009). Despite the lack of hypertension, plasma creatinine levels are increased (Moritz et al. 2009). Whether glomerular filtration rate (GFR) is altered in hypertensive female growth-restricted offspring at 12 months of age in the model of induced by a reduction in uterine perfusion in the rat is not yet known. However, GFR does not differ in male or female growth-restricted rats at 3 months of age relative to control in this model when male growth-restricted rats exhibit overt hypertension whereas female growth-restricted rats remain normotensive (Alexander 2003). Hypertension in female growth-restricted offspring in the model of programming induced by reduced uterine perfusion is associated with an increase in adiposity (Intapad et al. 2013). Whether female growth-restricted offspring induced via bilateral uterine ligation exhibit an increase

in adiposity that develops with age is not reported. Thus, programmed differences in adiposity that occur with age may contribute to the difference in susceptibility to age-dependent hypertension in these different models of IUGR. Yet, further studies are needed to determine the exact mechanisms that mediate the increase in blood pressure that occurs with age in female growth-restricted rats and to also determine why subtle differences in the method of developmental insult program differing outcomes with age.

Other models of developmental insult also demonstrate an enhanced susceptibility to impaired blood pressure regulation that occurs with age, an observation that is not limited to female offspring. Although overt hypertension is not observed in young adult male rats exposed to nicotine during prenatal life, blood pressure is markedly increased with age (findings reported at 22 months of age) relative to age-matched control counterparts (Tao et al. 2013). Female offspring exposed to nicotine during prenatal life develop an enhanced sensitivity to acute Ang II at 22 months of age that is not present in young adulthood (Tao et al. 2013). However, female rats in this model remain normotensive at 22 weeks of age (Tao et al. 2013) indicating that females are less susceptible to the impact of age in the developmental programming of impaired blood pressure regulation. Thus, this study indicates that age impacts susceptibility to the developmental programming of hypertension. In addition, this study suggests that male and female offspring exposed to a developmental insult may demonstrate a difference in age-induced susceptibility to impaired blood pressure regulation that has its origins in early life and provides merit for additional studies to investigate the impact of age and sex in the developmental origins of health and disease.

Renal sympathetic nervous system activation

Obesity is a major risk factor for hypertension with an increase in sympathetic nervous system (SNS) activation serving as the link between the increase in adiposity and the increase in blood pressure (da Silva et al. 2013). Leptin, a hormone released by adipocytes, promotes SNS activation suggesting leptin may be a key mediator linking obesity and hypertension (da Silva et al. 2013). Female growth-restricted offspring in the model of developmental insult programmed by placental insufficiency in the rat develop an increase in adiposity associated with a marked increase in circulating leptin and hypertension by one year of age (Intapad et al. 2013). Renal denervation abolishes hypertension in female growth-restricted offspring at one year of age (Intapad et al. 2013) implicating a critical role for the renal nerves and activation of the SNS in the development of age-dependent hypertension in this model. Renal denervation also abolishes hypertension in male-growth restricted rats at 3 months of age (Alexander et al. 2005) further suggesting an important role for activation of the SNS in the etiology of programmed hypertension in this model of developmental insult induced via placental insufficiency. Yet, male growth-restricted offspring that are hypertensive in young adulthood do not exhibit an increase in total fat mass suggesting that the stimulus for activation of the SNS in this model not only differs in male versus female growth-restricted rat, but is also age dependent. Thus, a key role for the SNS is indicated in the etiology of developmental programming of hypertension. Additional studies are required to clearly elucidate the origins of SNS activation and its contribution to hypertension that originates from adverse influences during early life.

Conclusion

Experimental studies indicate that development insults exert sex-specific programming of nephron number and blood pressure in males and females (Figures 1a and 1b). The exact mechanism(s) involved remain unclear, but appear to be multi-factorial. The impact of the hormonal milieu on regulatory systems key to blood pressure regulation may contribute to sex differences in programmed outcome (Figure 1). Modulation of the intrarenal RAS via sex hormones may confer increased susceptibility (Figure 1a) or protection against the hypertension in a manner that is sex-specific (Figure 1b). Furthermore, innate sex differences in oxidative stress or the endothelin system may contribute to sex-specific programming of blood pressure (Figures 1a and 1b). Age may also lead to sex-specific development of cardiovascular risk factors such as adiposity (Figure 1b) following a developmental insult and contribute to the sex difference in blood pressure that has its origins in early life. In addition, recent studies indicate that age can impact the long-term control of blood pressure following a developmental insult and indicate that susceptibility to programming of impaired regulation of blood pressure and hypertension increases with age in the male and female offspring. Further studies are needed to clarify the importance of sex in the developmental programming of hypertension and impaired blood pressure regulation.

Physiological relevance

Experimental studies indicate that sex differences in blood pressure programmed in response to an adverse influence during fetal life may involve sex-specific modulation of the RAS, oxidative stress, and endothelin. Animal models investigating the pathophysiology of sex differences in the developmental programming of hypertension implicate the importance of acknowledging that men and women may present a sexual dimorphism in their risk to develop hypertension and coronary heart disease. Importantly, sex differences in mechanistic pathways that contribute to the developmental programming of hypertension may influence potential therapeutic strategies and interventions in the health assessment of individuals born low birth weight.

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Figure 1a

Figure 1b

Figure 1.

Potential mechanisms by which a developmental insult differentially programs the long-term control of blood pressure in males (a) and females (b). Mechanisms may be due to the influence of the hormonal milieu on the renin angiotensin system (a and b), due to innate sex differences in production of reactive oxygen species or endothelin (a and b), or impacted by increased susceptibility that occurs with age and the development of age-dependent increases in adiposity leading to activation of the sympathetic renal nerves (b). The fetus also exhibits innate sex differences in expression of the intrarenal renin angiotensin system which may (a and b) or may not reduce nephron number (b).