Insights into sympathetic nervous system and GPCR interplay in fetal programming of hypertension: a bridge for new pharmacological strategies

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Cardiovascular diseases (CVDs) are the most common cause of death from noncommunicable diseases worldwide. In addition to the classical CVD risk factors related to lifestyle and/or genetic background, exposure to an adverse intrauterine environment compromises fetal development leading to low birth weight and increasing offspring susceptibility to develop CVDs later in life, particularly hypertension – a process known as fetal programming of hypertension (FPH). In FPH animal models, permanent alterations have been detected in gene expression, in the structure and function of heart and blood vessels, compromising cardiovascular physiology and favoring hypertension development. This review focuses on the role of the sympathetic nervous system and its interplay with G-protein-coupled receptors, emphasizing strategies that envisage the prevention and/or treatment of FPH through interventions in early life.

Introduction

Cardiovascular diseases (CVDs) are the main cause of mortality and morbidity from noncommunicable diseases worldwide; and >75% of deaths occur in low- and middle-income countries [1]. Together with the already known CVDs risk factors related to lifestyle (being sedentary, unhealthy diet, smoking tobacco) and genetic background, the importance of fetal life is well recognized [2–4]. The fetus can adapt to adverse intrauterine conditions, such as malnutrition, oxygen deprivation, placental insufficiency and exposure to excess glucocorticoids (GCs) or toxic substances, to ensure survival [5–7]. However, these conditions induce alterations in fetal development that result, later in life, in an increased susceptibility to develop CVDs, a phenomenon named developmental origins of health and disease (DOHaD) or fetal programming.

David Barker was the first to advocate the hypothesis that adaptive responses of the fetus to maternal undernutrition (MUN) resulted in low birth weight (LBW) and, in adult life, in the development of coronary heart disease and hypertension [2,8]. Over the past years, several epidemiological studies in populations exposed to starvation and/or intrauterine stress have validated Barker's hypothesis, demonstrating an association between LBW and increased blood pressure (BP) in adult life – a process known as fetal programming of hypertension (FPH) [6,9–11].

MUN seems to be the major cause of LBW in underdeveloped or developing countries, whereas in high-income societies LBW is mostly related to prematurity or obstetric complications associated with delayed pregnancy. For example, placental insufficiency, causing placental hypoxia and fetal oxygen delivery privation [12,13], and pre-eclampsia are conditions related to increased maternal age [14,15] that associate with offspring hypertension in adult life [15]. Excess fetal exposure to GCs could also contribute to LBW [16], which is clinically relevant, because women with risk of preterm delivery are treated with CGs to improve fetal pulmonary function and reduce mortality. Besides, maternal psychological stress could abnormally elevate cortisol levels [17]. Cortisol access to the fetus is limited to the placental barrier owing to its conversion by 11-β hydroxysteroid dehydrogenase 2 into cortisone. However, this enzyme can be reduced in adverse fetal

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conditions [18], favoring cortisol access to the fetus. Other stress factors, such as exposure to toxic substances (alcohol, tobacco) or environmental pollutants, can also affect fetal development, contributing to FPH [19–21].

Despite the efforts carried out so far, the mechanisms underlying the predisposition to FPH are not completely understood. Nevertheless, increasing evidence has shown the implication of oxidative stress [22,23], the renin–angiotensin system (RAS) [24–26] and the sympathetic nervous system (SNS) [27–29], as well as alterations in the GCs axis [6,30–32]. Some of these alterations seem to be mediated by epigenetic modulation of genes implicated in cardiovascular control [33–36]. Altoghether, these aspects can contribute to FPH development (Fig. 1).

Experimental data gathered in animal studies have been very valuable to understanding the relationship between adverse intrauterine environment and increased susceptibility to hypertension. Among others, the most common animal models mimicking the different fetal stress factors are maternal nutritional restriction during pregnancy or lactation (protein, global nutrients, vitamins, etc.), exposure to hypoxia, placental insufficiency or treatment with GCs [37,38].

In these animal studies, high BP is associated with changes in blood vessels (remodeling, stiffening and endothelial dysfunction), heart (cardiomyocyte hypertrophy or intramyocardial fibrosis) and kidneys (low nephron number, alterations in sodium handling, etc.) [6,39–42]. These studies have also evidenced the important influence of sex in FPH – male offspring from all the above-mentioned experimental models develop hypertension by adult age, whereas females remain normotensive or develop milder forms of hypertension [43]. This sexual dimorphism has been proposed to be related to the protective effects of estrogens on the cardiovascular system [44,45]. In addition, the concept of 'sex of the placenta' has also been put forward and it has been suggested that the placenta nourishing a female fetus could adapt better to adverse intrauterine environments; thus, contributing to the lower impact of FPH in females [46,47]. Despite the fact that, in animal models of FPH, the role of sex has been well documented, in humans this is not so evident. This discrepancy is probably related to differences in the age of the populations under study and the confounding factor of menopause [44,48].

SNS and fetal programming of hypertension

SNS has an integral role in the regulation of heart rate and contractility, vascular tone and fluid volume. Excessive sympathetic nerve activity (SNA) has deleterious effects namely increased cardiac output, peripheral resistance and retention of salt and water; thus, contributing to the development and/or maintenance of hypertension [49–53]. In vessels, increased SNA is responsible for vascular remodeling related to smooth-muscle hypertrophy and fibrosis [54].

Data from humans and experimental animal models of hypertension support the neurogenic hypothesis of hypertension, which considers SNA as the primary factor underlying the elevation of BP [55–58]. Although the main causes of increased SNA remain undefined, alterations of reflexes and/or metabolic factors have been proposed as candidates [58].

In several animal models of FPH, altered SNS control is evident. In offspring of maternal low-protein-diet (MLPD) rats, hypertension was associated with increased cardiovascular sympathetic tone [59], whereas no baroreflex dysfunction was found [60]. Offspring from rats exposed to intermittent hypoxia at the end of pregnancy exhibit increased BP related to an altered sympatho–vagal balance [61]. Also, in MLPD rat offspring, increased SNA was reported in response to physical stress induced by activation of exercise pressor reflex [62], most probably owing to an exaggerated increase in renal SNA [63]. Another FPH rat model (induced by hypoxia *in utero*) showed an increased muscle SNA and a hypersympathetic innervation in skeletal muscle arteries [28].

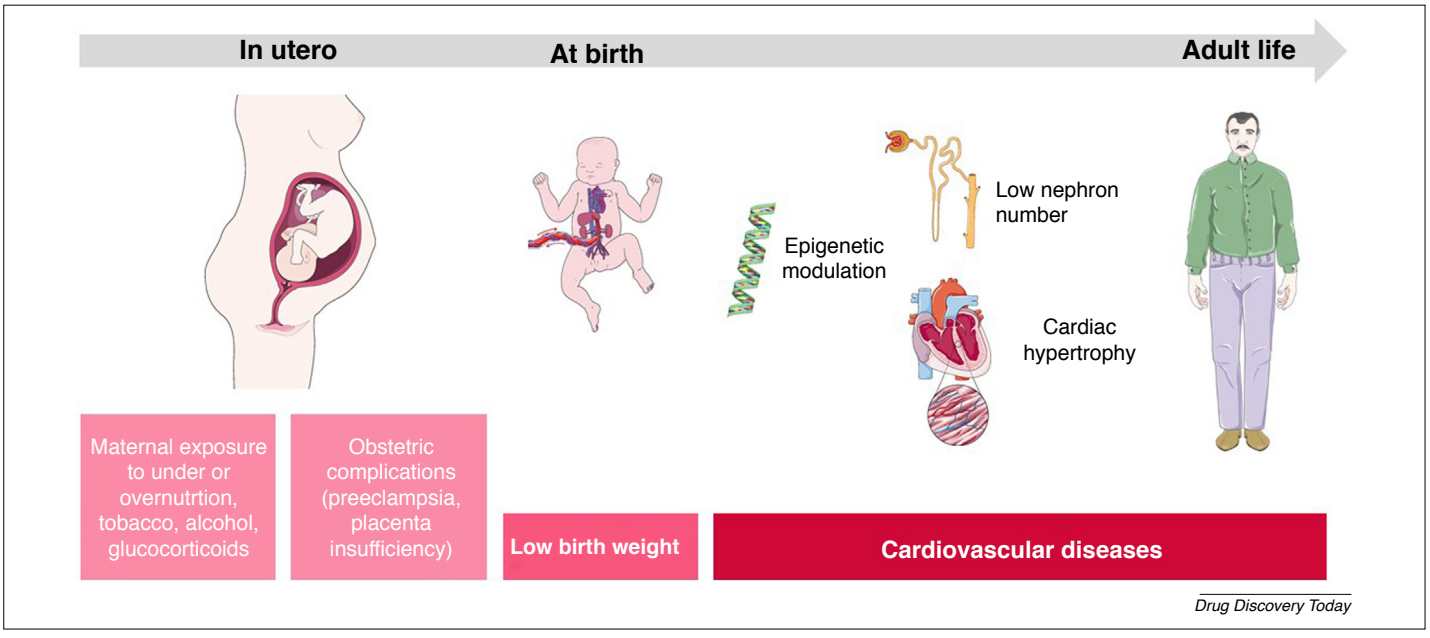

FIGURE 1

The developmental programming of cardiovascular disease hypothesis. Figure made with graphic components obtained from the website: https://smart.servier.com.

Another alteration corroborating an abnormal SNS control in FPH rats is the elevation of catecholamines in the cardiovascular system, owing to increased release or biosynthesis. In FPH rats induced by placental insufficiency or MLPD, circulating catecholamines were raised in the fetus and in adult offspring, possibly because of increased SNA [29,64,65]. In this sense, an increased electrically evoked noradrenaline output has been reported in mesenteric arteries from MUN rat offspring [66]. Besides, there is evidence of elevated catecholamine biosynthesis due to increased expression of adrenal phenylethanolamine *N*-methyltransferase (PNMT), in dexamethasone exposure during gestation rat offspring [67]. Elevated PNMT mRNA expression was also detected in spontaneously hypertensive rat (SHR) brain [68].

In addition to alterations at the peripheral level, data also indicate changes in central SNA. An elevated basal and stimulated dopamine output has been described in rat offspring exposed to prenatal stress [69]. Significant SNA alterations were also found in the nucleus *tractus solitarius* [62], hippocampus and hypothalamic paraventricular nucleus from MUN rat offspring, with a marked activation of the hypothalamo-pituitary-adrenal axis [30]. Changes in central SNA could be related to alterations in redox balance. Oxidative stress is known to contribute to FPH, through many mechanisms (for details, see review [23]), but the relevance of SNA in redox status and *vice versa* has been recently highlighted. For example, in SHR, oxidative stress contributes to an increased SNA [70] and MUN rat offspring exhibit changes in brainstem redox status accompanied by an increase in SNA [71]. Excess cortisol levels can also contribute to FPH through the SNS. For example, in sheep fetuses it has been shown that adrenal GCs contribute to cardiovascular regulation by modulation of SNA and arterial baroreflex [72].

In LBW humans, there is also evidence of altered SNA [73,74]. Children with LBW, owing to prematurity or small for gestational age, excrete high catecholamine levels [75], which has been associated with longer periods of tachycardia during stress exposure [76]. LBW is also associated with exaggerated BP responses to psychological stressors, related to alterations in baroreflex control [77] and greater SNA response [76]. Young men and women born with LBW also exhibit raised muscle SNA [73] and exaggerated sympathetic discharge in response to muscle metaboreflex [78]. Abnormalities in heart rate and baroreflexes are also observed in premature infants, related to the immaturity of their autonomic nervous system [79], which could contribute to increased cardiovascular risk in this population [80]. Taken together, data are consistent with a pathophysiological role of the SNS in FPH, with evidence indicating the occurrence of an increased SNA.

G-protein-coupled receptors and FPH

G-protein-coupled receptors (GPCRs) are a large family of seven-transmembrane-domain proteins activated by several peptides or proteins, such as neurotransmitters and hormones [81]. GPCRs trigger intracellular signal transduction pathways and influence several physiological functions, including cardiovascular control [82]. Indeed, some GPCRs are involved in the modulation and regulation of vasodilator and vasoconstrictor responses; thus, influencing vascular responsiveness and BP control. Dysregulation of GPCR-mediated mechanisms during fetal life can be implicated in FPH. Among possible mechanisms, we can include changes in the receptor itself or in the intracellular mechanisms or even in the concentration of receptor ligands. All these changes can lead to an upregulation or downregulation of GPCRs, which can modify endocrine and nervous responses involved in BP control. Below, we discuss evidence of alterations of key GPCRs, namely adrenoceptors, angiotensin, adenosine and endothelin receptors in FPH (Fig. 2).

Adrenoceptors

Noradrenaline released from sympathetic nerves can activate α- or β-adrenoceptors modulating postsynaptic nerve or vascular responses with both types described as being involved in FPH. Indeed, studies in rats provide evidence of the implication of α-adrenoceptors localized in the central SNS in FPH: the natriuretic effect induced by central noradrenaline injection was abolished by α_1-adrenoceptor antagonist (prazosin) in MLPD rat offspring [83]; administration of α_2-adrenoceptor antagonist (yohimbine) normalized urinary sodium excretion and reduced BP in FPH offspring [83]. Conversely, β-adrenoceptors can also contribute to FPH: in 2-week-old MUN rat offspring, the myocardial mRNA expression of β_2-adrenoceptors was increased, which might explain the increased susceptibility to ischemia–reperfusion injury [84]. In humans, recently, the involvement of adrenoceptors in FPH has been suggested because α-adrenoceptor blockade attenuated the development of hypertension in preeclampsia [85]. Taken together, the information is in agreement with a relevant role of adrenoceptors in FPH.

Angiotensin receptors

Contribution of angiotensin receptors (ATRs) to FPH has been demonstrated in animals exposed to nutritional insults such as low-protein, high-fat or sugar diets [86–88], toxins such as nicotine [89,90] or to CGs [91]. Accumulating evidence in rats indicates that AT1R and AT2R expression is altered in response to several fetal stressors. An upregulation of AT1R expression was found in the kidneys [24] and mesenteric vasculature [66] from MUN rat offspring and in the brain of adult rats exposed to MLPD [92] or to nicotine [90] during fetal development. Similarly, increased pulmonary AT1R expression was found in lungs of mice exposed to hypoxia [93] and in the kidney of near-term ovine fetuses exposed to high altitude [94]. Regarding AT2R expression, a downregulation was shown in the kidney of offspring of MUN, MLPD [26,95], hypoxia [94] and fetal exposure to GCs [96].

Epigenetic and gene expression changes are responsible for many alterations in FPH [36], some of them associated with RAS. MLPD led to an increased AT1R gene expression and subsequent upregulation of AT1R in adrenal glands from adult rat offspring, ultimately contributing to the development of hypertension [35]. Maternal GC exposure in early pregnancy can induce changes in methylation and expression of the AT1R gene. In addition, in prenatal high sucrose exposure aged offspring, mRNA and protein expression of the AT1R gene were significantly increased in large and small blood vessels, which could be closely associated with the changes of epigenetic mechanisms such as histone modifications [97]. In brain MLPD mouse offspring, an upregulation of mRNA expression of angiotensinogen and angiotensin-converting enzyme (ACE) and a downregulation of mRNA levels of AT2R were reported [98]. ACE is another RAS player

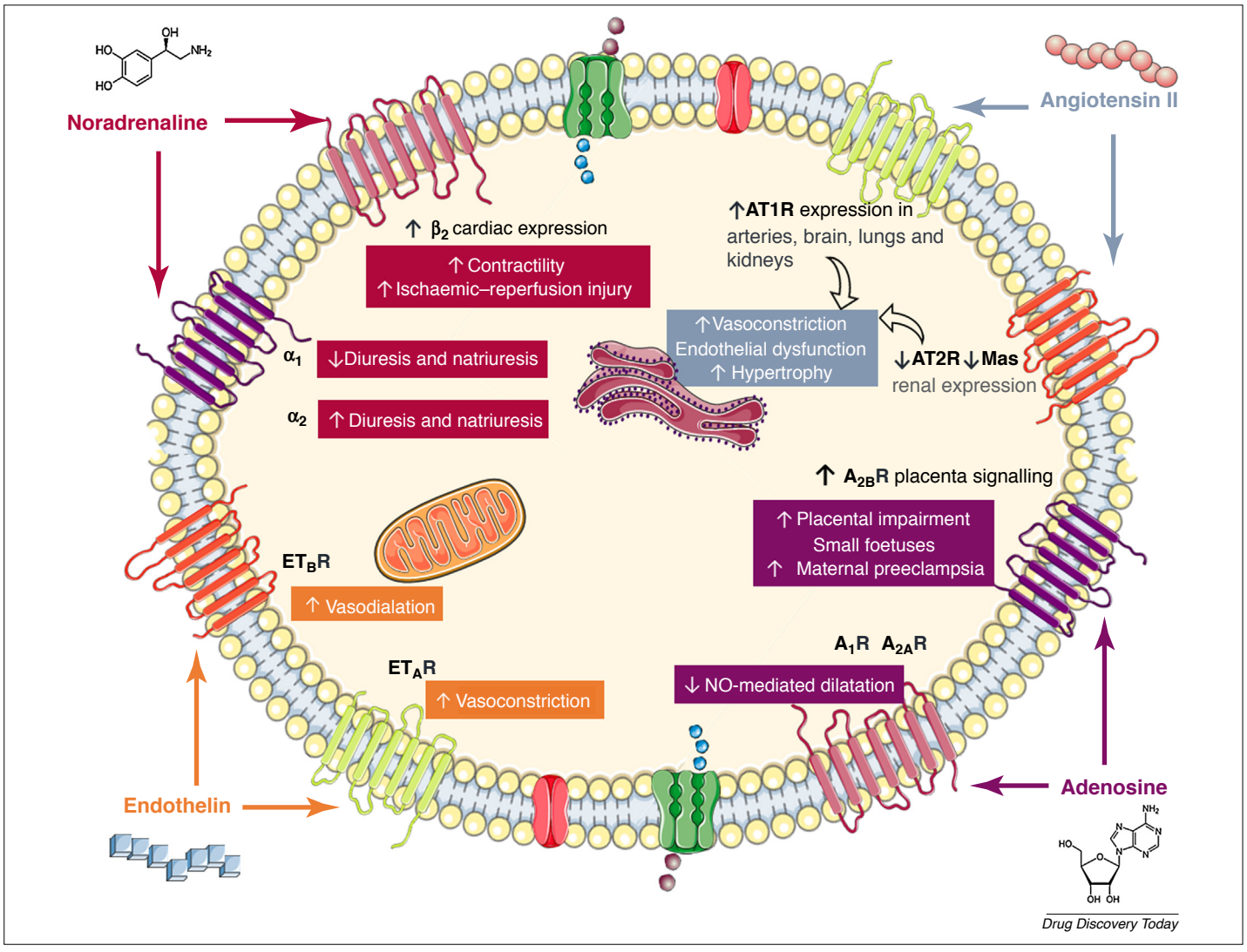

FIGURE 2

Schematic representation of the involvement of adrenoceptors, angiotensin II, adenosine and endothelin receptors in fetal programming of hypertension (FPH). Figure made with graphic components obtained from the website https://smart.servier.com.

modified in FPH. Pulmonary and plasma ACE activities seem to be increased in MUN adult rat offspring [99].

In experimental FPH, hypertension was controlled after treatment with ACE inhibitors or ATR antagonists [25,99,100], similarly to what occurs in essential hypertension. The above studies evidence the role of the classical ACE/angiotensin II (Ang II)/AT1R/AT2R axis in FPH. Recently, the nonclassical ACE2/Ang-(1–7)/Mas receptor axis was also suggested to be implicated [101], as shown by the altered Ang-(1–7) system within the brain and in the kidney of rats exposed to GCs in fetal life, proving the contribution to cardiovascular dysfunction.

In humans exposed to adverse intrauterine conditions, information is still scarce regarding ATRs or other RAS players. Nevertheless, children born from preeclamptic pregnancies have increased circulating levels of aldosterone [102]. Also, boys with LBW exhibited a significant increase in ACE activity and circulating Ang II, which were associated with increased systolic BP [103]. However, this association was not found in girls, supporting the existence of sex differences in FPH also in humans. Indeed, RAS alterations associated with FPH seem to be age- and sex-specific [37,91]. Overall, experimental data are consistent and support the idea that RAS might be a common mechanism that underlies hypertension of developmental origins.

Adenosine receptors

Considerable evidence supports the involvement of adenosine and its receptors (A_1R, A_{2A}R, A_{2B}R and A_3R) in hypertension [104,105]. Adenosine is a key signaling molecule that coordinates a rapid multicellular physiological response to hypoxia or tissue damage. Indeed, chronic systemic hypoxia *in utero* affects cardiovascular responses in adult rat offspring through an A_1R-mediated mechanism [106]. These rats have functional A_1R in the heart and vasculature but show attenuated adenosine release and endothelium-dependent vasodilation [106].

In humans, adenosine is a determinant in pregnancy diseases associated with altered umbilical blood flow, namely preeclampsia [107,108]. Alterations in enzymes involved in adenosine bioavailability, such as increased placental 5′-nucleotidase and reduced

placental adenosine deaminase, favor high placental adenosine levels, which, coupled with an enhanced $A_{2B}R$ receptor signaling, could contribute to preeclampsia pathogenesis [109]. Furthermore, in women with preeclampsia, it has been proposed that reduced angiogenesis mediated by adenosine might be associated with the development of hypertension in the offspring [110]. Altogether, this information points toward a relevant role for the adenosinergic system in FPH.

Endothelin receptors

Endothelin 1 (ET-1), mainly released from endothelium, can activate endothelin receptor type A (ET_AR) and type B (ET_BR). These receptors exert opposite cardiac and vascular effects: ET_AR mediates vasoconstriction whereas ET_BR mediates vasodilation [111,112]. In the context of FPH, few pieces of work establish a role for ET-1 and/or its receptors.

Hypoxia [113] and MUN [39] rat offspring present an enhanced vasoconstriction to ET-1. In rat offspring exposed to fetal hypoxia, treatment with tezosentan, an $ET_{A/B}R$ antagonist, caused a significant reduction in BP [113]. The selective ET_AR antagonist ABT-627 reduced BP in FPH rats, accompanied by a disruption in ET-1 expression [114]. These studies encourage further clarification regarding the usefulness of endothelin receptors as targets to treat or prevent FPH. Despite this, recent efforts on endothelin receptor antagonists envisage their putative use for the treatment of resistant hypertension [115]. Nevertheless, more studies are required to completely understand the implication of GPCRs in the development and maintenance of hypertension of fetal origins.

Interplay between the SNS and GPCRs in FPH

SNA can be influenced by different GPCRs, because these receptors can modify noradrenaline bioavailability in the synapsis and/or interact with signaling cascades. Furthermore, altered SNA can also influence GPCR activation by modifying their expression or conditioning its own signaling events. In FPH, increased SNA has been associated with hypersympathetic innervation and/or with alterations in specific GPCR expression or function. These changes condition vascular responsiveness or renal function and can contribute to increased BP (Fig. 3). The association between FPH animal models and the experimental results related to SNS and GPCRs are summarized in Table 1.

Interventions to counteract FPH

Understanding the causative mechanisms of FPH could provide new opportunities and challenges for prevention through early-life interventions. First, pharmacological treatments or lifestyle changes during pregnancy might help to reduce programming. Second, early interventions in the offspring during key developmental windows, such as lactation, could also help to reduce the impact of CVDs in future generations.

Pharmacological or nutritional interventions with antioxidants are a plausible strategy because oxidative stress is one of the underlying mechanisms in FPH, common to different fetal stressors, namely malnutrition [116], exposure to toxic substance(s) [117,118] or GCs [119]. Studies in animal models have provided proof of the effectiveness of antioxidant treatments, in pregnancy, against FPH. In hypoxic pregnancies, treatment with vitamin C improved transplacental oxygenation [120]. In addition, melatonin and *N*-acetylcysteine administration during the entire pregnancy and lactation have demonstrated effectiveness against the development of hypertension in an FPH rat model induced by NG-nitro-L-arginine-methyl ester during gestation [121]. Resveratrol also has promising effects for the treatment of feto–placental flow alterations in preeclampsia, owing to its anti-inflammatory

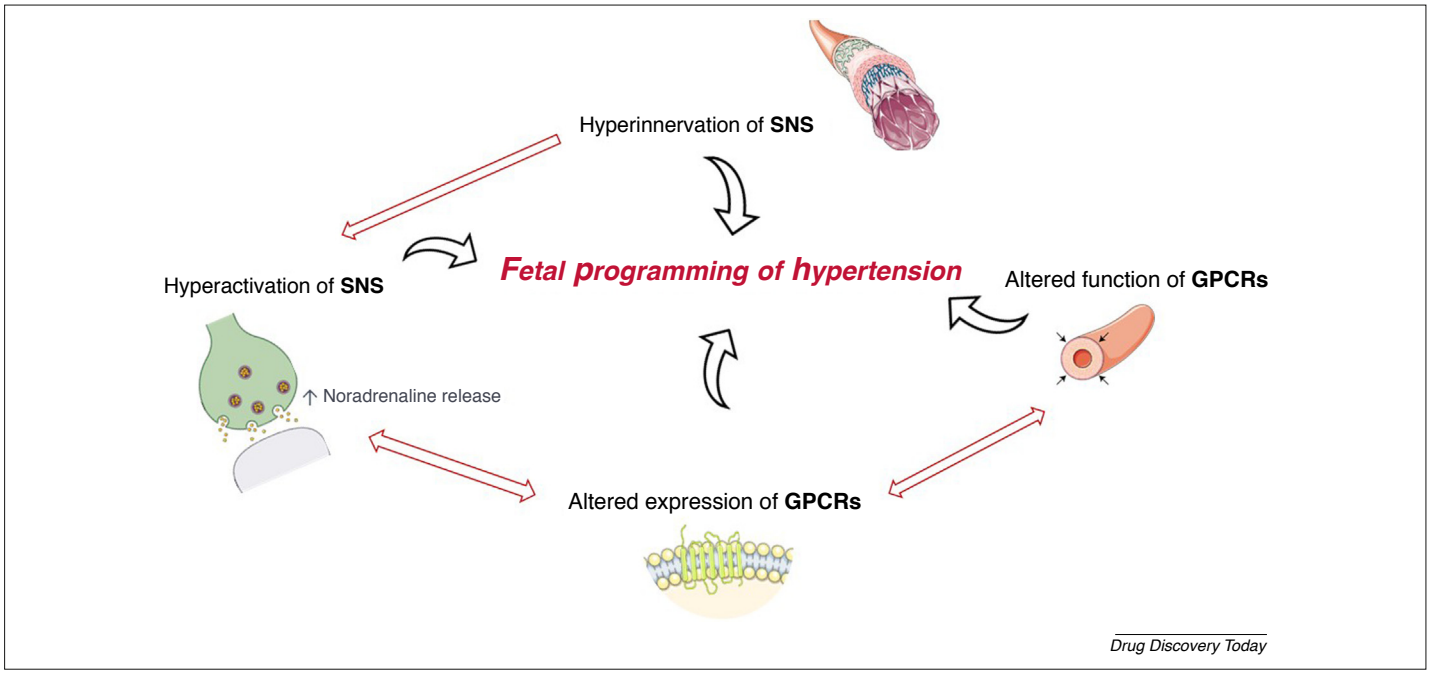

FIGURE 3

Role of the sympathetic nervous system (SNS) and its interplay with G-protein-coupled receptors (GPCRs) in fetal programming of hypertension (FPH). Figure made with graphic components obtained from the website https://smart.servier.com.

TABLE 1

Fetal programming of hypertension (FPH)-mediated mechanisms associated with respective G-protein-coupled receptor (GPCR) and mediator levels dysregulation in experimental FPH models

Animal model of FPH	Mechanism mediated by FPH	Mediator level alterations	GPCR dysregulation	Sex dependence	Refs
Maternal cocaine exposure	Reprogramming of vascular reactivity led to ↑ risk of hypertension in adult offspring	↑ NA in the synaptic cleft	α2-adrenoceptor upregulation in the hippocampus, amygdala and parietal cortex	Males	[132,133]
Maternal low protein diet	↑ RAS activity; ↑ sympathetic outflow in the kidney led to ↑ BP	↑ Ang II	↑ AT1R expression receptors in kidneys and brain	Males	[39,89,134]
Maternal undernutrition	Hypersympathetic activation related to a tonic facilitation of prejunctional AT1R receptors by endogenous Ang II	↑ Ang II	↑ AT1R function in mesenteric and tall arteries ↑ AT1R expression receptors in mesenteric artery	Males	[64]
Maternal chronic hypoxia exposure	↑ muscle sympathetic nerve activity induced by endogenous adenosine ↑ density of sympathetic innervation of arterial vessels ↑ ROS exert a tonic vasoconstrictor influence on muscle	↓ adenosine ↓ NO	↓ A_1R function	Males	[135]

Abbreviations: NA, noradrenaline; RAS, renin–angiotensin system; BP, blood pressure; Ang II, angiotensin II; AT1R, angiotensin receptor type 1; AT2R, angiotensin receptor type 2; ROS, reactive oxygen species; A_1R, adenosine receptor type 1.

and antioxidant properties *in vitro* [122]. In MLPD rat offspring, resveratrol administration during pregnancy partially prevents oxidative stress and metabolic dysfunction [123]. In the same animal model, prenatal treatment with lazaroid, a lipid peroxidation inhibitor, abolished the increased Ang-II-mediated contractile response and prevented the increase in BP [124]. Also, tempol avoided the BP increase in adult mice of FPH induced by GC exposure [125].

In humans, pregnancy alterations, such as preeclampsia, that program the offspring are also related to oxidative unbalance. In low- and middle-income countries, micronutrient dietary deficiencies can contribute to fetal programming through oxidative stress [14]. In these settings, nutritional interventions with vitamins or minerals during pregnancy have been demonstrated to be an effective approach to reduce the risk of prematurity and LBW [126] and to improve offspring cardiometabolic health [127]. In high-income societies, the main problem is the obstetric complications that alter placental function leading to LBW and premature births (and subsequent need for GC treatment). We have previously evidenced the association between a low antioxidant status in early pregnancy and the later development of obstetric complications [14]. Therefore, antioxidant treatment can be a useful strategy to reduce preeclampsia and other placental disorders once antioxidant deficiency in pregnancy increases oxidative damage and compromises feto–placental flow through nitric oxide (NO) inactivation by reactive oxygen species. In fact, several antioxidants, namely *N*-acetylcysteine, vitamin C or melatonin, as well as NO donors like L-arginine, have been used in women with pregnancy complications with variable results; but most of them have shown benefits and safety [128]. The above-mentioned data suggest that antioxidant therapy, either through nutritional or pharmacological interventions, could be a strategy to counteract or reduce FPH.

A second possible developmental window to counteract the effects of FPH is the lactation period. In this regard, drugs used to treat hypertension have been studied in experimental animal FPH offspring concerning their putative usefulness to modulate the development of hypertension postnatally. Administration of nifedipine (calcium channel blocker) in FPH offspring at 4–12 weeks did not modify BP [100], discarding the use of this pharmacological group for this purpose. However, in MLPD rat offspring and in rats exposed to placenta insufficiency, at 2–4 weeks old, captopril and enalapril (ACE inhibitors) treatment (initiated after weaning) prevented the development of hypertension, with animals remaining normotensive at least for 12 weeks after treatment suppression [25,99,100,129]. This is corroborated also in MUN rat offspring, because treatment with aliskiren or losartan – an AT1R antagonist – administered between 2 and 4 weeks of postnatal life, prevented the development of hypertension until 12-weeks old [130]. Treatment with AT1R antagonists such as losartan [100] or candesartan [131] was also effective in preventing the development of hypertension in MUN adult rat offspring. Candesartan not only lowered BP but also protected against cardiac enlargement and coronary perivascular fibrosis [131]. However, this therapeutic strategy could only be implemented after birth, owing to the teratogenic effects ascribed to this group of drugs during pregnancy and their impact avoiding adequate nephrogenesis.

After birth, vitamin C and E treatments reverse the increased vasoconstrictor responses in FPH rats [132] and allopurinol, a xanthine oxidase inhibitor, had analogous effects [133]. Coenzyme Q decreased oxidative stress and DNA damage in the aorta of FPH offspring [134] and resveratrol improved insulin sensitivity, vascular function and prevented cardiac dysfunction and hypertrophy [135,136]. Therefore, antioxidant therapy should be considered, alone or in association with other drugs, in FPH.

In humans, breast milk is an important source of antioxidants and other bioactive compounds; thus, breast-feeding could help to counteract the negative effects of oxidative stress in newborns, particularly in preterm infants that exhibit deficiency of antioxidant systems, and are at higher risk of FPH [137]. Regarding pharmacological intervention, research is needed to analyze the reverting effect of treatments on FPH with drugs binding to GPCRs. Currently, several drugs are at the forefront to be used in FPH but no ongoing clinical trials are being performed, so far, with this particular purpose.

Concluding remarks

Data collected so far suggest that FPH is related to the exposure to stress factors during pregnancy and subsequent LBW; and will probably continue to contribute to the burden of CVDs in the coming decades. In this context, determining the main mechanisms implicated is imperative, namely those related with sex differences. Thus, therapeutic approaches targeted properly to these sex differences could offer the best opportunity to mitigate the progression of CVD in women and men. In addition, increasing evidence supports the implication of increased SNA eventually linked to some GPCRs, which modify the bioavailability of noradrenaline in synapsis and/or interact with signaling cascades, ultimately conditioning renal, cardiac and vascular responses. This knowledge will open the door to risk stratification for the development and definition of new preventive and/or therapeutic strategies.

Conflicts of interest

The authors report no conflicts of interest.

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