*Review*

# Gasotransmitters for the Therapeutic Prevention of Hypertension and Kidney Disease

Chien-Ning Hsu [1,2] and You-Lin Tain [3,4,*]

1   Department of Pharmacy, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung 833, Taiwan;
    cnhsu@cgmh.org.tw
2   School of Pharmacy, Kaohsiung Medical University, Kaohsiung 807, Taiwan
3   Department of Pediatrics, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College
    of Medicine, Kaohsiung 833, Taiwan
4   Institute for Translational Research in Biomedicine, College of Medicine, Kaohsiung Chang Gung Memorial
    Hospital and Chang Gung University, Kaohsiung 833, Taiwan
*   Correspondence: tainyl@cgmh.org.tw; Tel.: +886-975-056-995; Fax: +886-7733-8009

**Abstract:** Nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide ($H_2S$), three major gasotransmitters, are involved in pleiotropic biofunctions. Research on their roles in hypertension and kidney disease has greatly expanded recently. The developing kidney can be programmed by various adverse in utero conditions by so-called renal programming, giving rise to hypertension and kidney disease in adulthood. Accordingly, early gasotransmitter-based interventions may have therapeutic potential to revoke programming processes, subsequently preventing hypertension and kidney disease of developmental origins. In this review, we describe the current knowledge of NO, CO, and $H_2S$ implicated in pregnancy, including in physiological and pathophysiological processes, highlighting their key roles in hypertension and kidney disease. We summarize current evidence of gasotransmitter-based interventions for prevention of hypertension and kidney disease in animal models. Continued study is required to assess the interplay among the gasotransmitters NO, CO, and $H_2S$ and renal programming, as well as a greater focus on further clinical translation.

**Keywords:** kidney disease; gasotransmitter; carbon monoxide; hypertension; developmental origins of health and disease (DOHaD); hydrogen sulfide; asymmetric dimethylarginine; heme oxygenase; nitric oxide

## 1. Introduction

Gasotransmitters, such as nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide ($H_2S$), are small gaseous molecules that penetrate membranes and play key roles in biology. Although these gases are toxic in excess, they are endogenously generated and exert specific biological functions at the physiological level [1–3]. A brief overview of their toxic and physiological levels is given in Table 1 [1–3]. Since it was identified as the endothelium-derived relaxing factor in the 1980s, NO has rapidly gained attention as one of the most important signaling molecules in the cardiovascular system [4]. A decade later, CO emerged as a gaseous vascular modulator of the cardiovascular system [5]. $H_2S$, next to NO and CO, has emerged as a third gasotransmitter with key roles in the regulation of cardiovascular and other systems [6]. All three gases have a significant impact on human health and potential value as a therapeutic target [1,2,4].

Chronic kidney disease (CKD) and hypertension are major non-communicable diseases, which are the leading causes of global deaths. According to the WHO, one in five women and one in four men have hypertension worldwide [7]. An estimated ~10% of the global population has CKD [8]. Hypertension and CKD are closely associated with an overlapping and interlinked cause and effect relationship [9], such that hypertension can lead to CKD progression and CKD is the most common cause of secondary hypertension. Of note, hypertension as well as kidney disease can take their origins in early

life, and when identified early, can be healed to prevent more associated disorders and serious complications.

**Table 1.** Physiological and toxic levels of NO, CO, and H$_2$S.

| | Physiological Level | Toxic Level | |
|---|---|---|---|
| **Gas** | **Blood Concentration** | **Exposure Limit** | **IDLH** |
| Nitric oxide (NO) | Low nM | TMA 25 ppm | 100 ppm |
| Carbon monoxide (CO) | nM–µM | TMA 35 ppm/C 200 ppm | 100 ppm |
| Hydrogen sulfide (H$_2$S) | High nM–low µM | C 10 ppm | 1200 ppm |

TWA = Time-weighted average; C = Ceiling; IDLH = Immediately dangerous to life or health concentrations; ppm = parts per million.

During kidney development, various early-life adverse environmental conditions can lead to hypertension and kidney disease in adulthood [10]. The idea was recently named "Developmental Origins of Health and Disease" (DOHaD) [11]. Conversely, through shifting therapeutic approach from adulthood to early life, namely, reprogramming, we have the potential to revoke disease processes before disease becomes apparent [12,13].

The three gases and their roles in established kidney disease and hypertension have been extensively reviewed elsewhere [4–6,14–17]. However, evaluating their impacts on hypertension and kidney disease of developmental origins has not been sufficiently addressed [18,19]. The aim of this review is to discuss, within the limits of present knowledge, how the three gasotransmitters are implicated in the developmental programming of hypertension and kidney disease. In particular, the review focuses on the potential of gasotransmitters for therapeutic prevention against hypertension and kidney disease of developmental origins.

We searched the PubMed/MEDLINE databases for studies published in English using the following search terms: "gasotransmitter", "kidney disease', "developmental programming", "DOHaD", "nitric oxide", "hydrogen sulfide", "carbon monoxide", "heme oxygenase", "oxidative stress", "nephron", "nephrogenesis", "mother", "pregnancy", "gestation", "offspring", "progeny", "reprogramming", and "hypertension". We also used the reference lists of identified articles to find additional studies. The last search was made on 30 May 2021.

## 2. Implications of Gasotransmitters in Pregnancy

A variety of adverse conditions during pregnancy can affect fetal development resulting in hypertension and kidney disease in adult offspring, including maternal malnutrition, maternal exposure to environmental chemicals/toxins, maternal illnesses, medication uses in pregnancy, etc. [10,12,13,20–22]. Gasotransmitters play a crucial role in the regulation of maternal hemodynamics, placenta vascular development, embryogenesis, feto-placental vascular reactivity, and fetal development during pregnancy [23–25]. Abnormalities of gasotransmitter production and signaling in compromised pregnancy are linked to adverse pregnancy and fetal outcomes. A drawing schematic summarizing the enzymatic production of NO, CO, and H$_2$S, and signaling pathways able to maintain normal pregnancy and fetal development are depicted in Figure 1. Each gasotransmitter is discussed in turn.
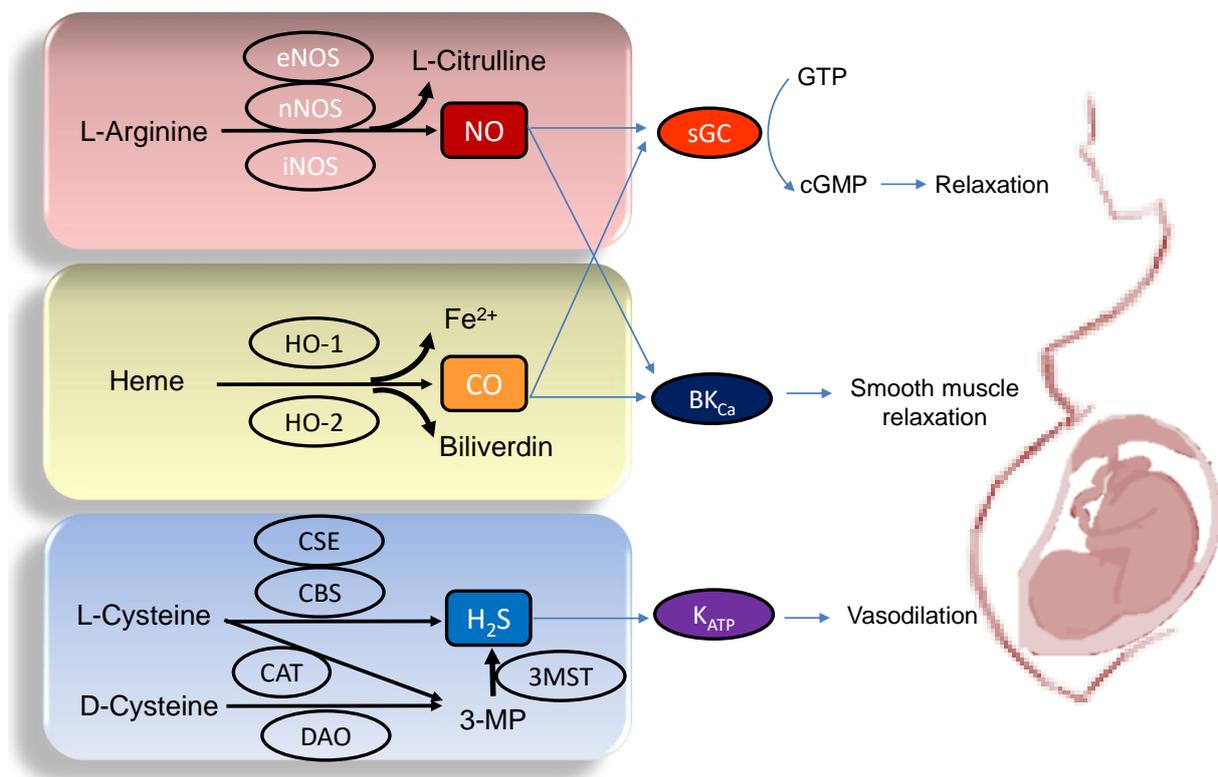
**Figure 1.** Schematic illustration of the enzymatic synthesis of NO, CO, and $H_2S$ and downstream signaling able to maintain maternal and feto-placental homeostasis. NO (upper panel) is formed by neuronal NOS (nNOS), endothelial NOS (eNOS), and inducible NOS (iNOS) from L-Arginine. Heme oxygenase-1 (HO-1) and -2 (HO-2) enzymes degrade heme to generate CO, iron, and biliverdin (middle panel). Three enzymes have been identified to enzymatically generate $H_2S$ (Lower panel), cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE), and 3-mercaptopyruvate sulphurtransferase (3MST). CBS and CSE produce $H_2S$ using L-cysteine. In an alternative pathway, 3-mercaptopyruvate (3-MP), the substrate for 3MST to produce $H_2S$, is provided by cysteine aminotransferase (CAT) using L-Cysteine and D-amino acid oxidase (DAO) using D-Cysteine, respectively. The blue arrow lines indicate downstream signals of gasotransmitters in the maintenance of homeostasis in pregnancy. NO and CO both can activate soluble guanylate cyclase (sGC) to increase cGMP, resulting in smooth muscle relaxation. The large-conductance $Ca^{2+}$-activated $K^+$ channel ($BK_{Ca}$) can also be regulated by NO and CO to elicit vasodilatation. Additionally, through the activation of ATP-sensitive $K^+$-channels ($K_{ATP}$), $H_2S$ can cause vasodilation in pregnancy.

## 2.1. Nitric Oxide

NO plays a vital role in the regulation of feto-placental circulation, fetal development, and transfer of nutrients from mother to fetus in normal pregnancy [26]. NO can be produced by L-Arginine–nitric oxide synthase (NOS)-dependent or NOS-independent pathways. There are three NOSs, namely, neuronal NOS (nNOS), endothelial NOS (eNOS), and inducible NOS (iNOS), which converts L-Arginine to L-Citrulline and generate NO (Figure 1). The NOS-independent pathway involves the reduction of nitrite to NO [27]. This nitrate–nitrite–NO pathway is considered as an alternative source of NO to the classical L-Arginine–NOS pathway. NO bioavailability mainly depends on intracellular L-Arginine concentrations [28]. There are two L-Arginine derivatives, asymmetric and symmetric dimethylarginine (ADMA and SDMA), which share common cationic amino acid transporters (CATs) with L-Arginine to move in and out of cells [29]. Both ADMA and SDMA can compete with L-arginine and inhibit NO production [29,30]. These two methylarginines are formed by a family of protein arginine methyltransferases (PRMTs) [29]. Dimethylarginine dimethylaminohydrolase-1 (DDAH-1) and -2 (DDAH-2) can metabolize ADMA to L-Citrulline and dimethylamine. In early pregnancy, the increase in NO and the concomitant reduction in ADMA assist hemodynamic adaptation and uterine relaxation,

to avoid disturbed intrauterine growth of the fetus. Conversely, NO-induced relaxation of the uterus in late pregnancy can be antagonized by physiologically increased ADMA levels to aid in preparing the uterine muscle fibers for the higher contractile activity that is required for successful delivery [31]. NO regulates the relaxation of vascular smooth muscle cells primarily by driving soluble guanylyl cyclase (sGC) to produce cyclic guanosine monophosphate (cGMP). Besides, NO-induced relaxation of human placental arteries is partly mediated through a direct effect on the large-conductance $Ca^{2+}$-activated $K^+$ channel ($BK_{Ca}$) [32].

Maternal plasma arginine levels were reduced in pregnancies complicated by intrauterine growth retardation (IUGR) [33]. Likewise, plasma arginine concentrations and placental eNOS abundance were decreased in women with preeclampsia [34]. Conversely, high ADMA levels in pregnant women are associated with preeclampsia [35], gestational diabetes mellitus [36], and fetal mortality [37]. Another line of evidence supporting NO deficiency in pregnancy attributed to adverse maternal and offspring outcome is from animal research. A previous report demonstrated that eNOS knockout pregnant mice displayed uteroplacental hypoxia, resulting in IUGR [38]. Additionally, adult rat offspring born of dams exposed to the L-N$^G$-Nitro arginine methyl ester (L-NAME, a NOS inhibitor) in pregnancy developed hypertension, proteinuria, and kidney disease [39,40].

### 2.2. Carbon Monoxide

Like NO, CO is a diatomic low molecular weight gas with similar molecular size and structure [41]. However, CO is a relatively non-radical, chemically stable gas. CO is produced endogenously as a by-product of heme degradation catalyzed by the action of heme oxygenase-1 (HO-1) or -2 (HO-2) enzymes. The two known CO signaling mechanisms are the cGMP-dependent and -independent pathways (Figure 1). Classical CO signaling is similar to NO signaling: CO activates sGC to increase cGMP stimulation of protein kinase G (PKG), resulting in smooth muscle relaxation. Although CO and NO bind sGC with similar affinity, NO-sGC is approximately 25–50 times more active than CO-sGC [42]. Besides, CO can directly enhance the activity of $BK_{Ca}$ in rat vascular smooth muscle cells through a cGMP-independent mechanism [24].

In pregnant women, low respiratory CO levels are associated with hypertension in pregnancy and preeclampsia [43]. CO has been shown to induce vasodilation of human placental resistance blood vessels via activation of sGC in vitro [44]. Additionally, deficiencies in HO-1 impair placenta development which have been associated with pregnancy disorders, such as recurrent miscarriages, IUGR, and preeclampsia [45].

### 2.3. Hydrogen Sulfide

Figure 1 illustrates major enzymes for $H_2S$ synthesis, including cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE), and 3-mercaptopyruvate sulfurtransferase (3MST) [6]. In the human placenta, these three enzymes are able to yield $H_2S$ [46]. CBS and CSE are cytosolic enzymes, but 3MST exists primarily in the mitochondria. Both CBS and CSE use L-Cysteine to generate $H_2S$. In an alternative pathway, 3-mercaptopyruvate (3-MP), the substrate for 3MST to produce $H_2S$, is provided by cysteine aminotransferase (CAT) and D-amino acid oxidase (DAO) [47]. In the peroxisome, D-Cysteine can be catabolized by DAO to generate $H_2S$ [17]. In addition to the enzymatic pathway, $H_2S$ can be produced via non-enzymatical pathway or by bacteria [48].

Uterine CBS and CSE levels increase during pregnancy and decrease during labor [24]. Like $BK_{Ca}$, uterine smooth muscle $K_{ATP}$ channel is important for uterine quiescence [49,50]. In humans, $H_2S$ can mediate vasodilation via $K_{ATP}$ channel to maintain feto-placental circulation [51]. During pregnancy, CBS and $K_{ATP}$ levels increase in human uterine artery smooth muscle cells [52]. However, decreased maternal $H_2S$ level and placental CBS and CSE protein levels relate to preeclampsia [51,53,54].

Collectively, NO, CO, and $H_2S$ play crucial roles for normal pregnancy. Dysregulated gasotransmitter signaling has been linked to preeclampsia, IUGR, stillbirth, and preterm

labor [24,25]. Although specific mechanisms mediating cellular and organismal changes in pregnancy due to gasotransmitters await further exploration, emerging evidences suggest their therapeutic potential for compromised pregnancy to improve maternal and fetal outcomes.

## 3. Implications of Gasotransmitters in Hypertension and Kidney Disease

### 3.1. Gasotransmitters and Hypertension

Several lines of evidence indicate that NO, CO, and $H_2S$ play key roles in the pathogenesis of hypertension. The first are observations on knockout mice lacking genes responsible for gasotransmitter synthesis. First, eNOS knockout mice displayed hypertension [55]. The importance of $H_2S$-generating enzymes in hypertension has also been demonstrated using CSE, CBS, or 3MST knockout mice [47,56–58]. Another report showed male HO-2 knockout mice are prone to develop renovascular hypertension [59].

The second line of evidences report dysregulated gasotransmitter signaling pathways in human and experimental models of hypertension. Prior research has addressed impaired L-Arginine–ADMA–NO pathway in the development of hypertension [60]. Dysregulated HO-1–CO pathway was reported to induce vascular dysfunction and hypertension in various animal models [61]. Likewise, deficiencies in $H_2S$-generating enzymes and/or activity in hypertension has been established in various animal models, including the NO-deficient rats [62], the Dahl salt-sensitive rats [63], the spontaneously hypertensive rat (SHR) [64], and the renovascular hypertensive model [65].

Third, several therapeutic strategies targeting different gasotransmitters have demonstrated to be significant promising for beneficial effects against hypertension in various animal models [60,61,66–68].

### 3.2. Gasotransmitters and Kidney Disease

The gasotransmitter generating enzymes iNOS, eNOS, nNOS, HO-1, HO-2, CSE, CBS, and 3MST were detected in kidney cells comprising podocytes, glomerular endothelial cells, tubular cells, and mesangial cells, but not all of them are constitutively expressed in every cell type [69,70]. For example, eNOS is expressed in the glomerular endothelial cells, peritubular capillaries, and vascular bundles, while nNOS is mainly detected in the tubular epithelial cells of the macula densa [70]. Of note, iNOS and HO-1 are not constitutively expressed in the kidney but only expressed under certain pathophysiological conditions like inflammation [70].

In the kidney, NO performs important signaling functions including the modulation of renal sympathetic neural activity, control of renal hemodynamics, regulation of pressure-natriuresis, blunting of tubuloglomerular feedback, and inhibition of tubular sodium reabsorption [70]. Accordingly, impaired NO signaling has been implicated in the pathogenesis of kidney diseases. As reviewed elsewhere [14,71], kidney injury is attributed to NO deficiency in a variety of CKD models, such as diabetic nephropathy, chronic glomerular nephritis, the 5/6 nephrectomy model, the aging kidney, the Zucker obese rat, chronic allograft nephropathy, etc.

The beneficial actions of CO in the kidney have also been recognized [15]. Inhibition of superoxide production, activation of sGC, stimulation of NO production, and stimulation of p38 mitogen-activated protein kinase (MAPK) pathway are all examples of the beneficial effects of CO in the kidney to protect the kidney [15]. Deficiency or inhibition of HO-1 in animal models worsens renal structure and function, while increased expression is protective [72]. So far, evidences from animal models indicate that several kidney diseases have been associated with impaired HO-1 or -2 system, including diabetic nephropathy [73], lupus nephritis [74], nephrotoxic nephritis [75], ischemia-reperfusion injury [76], obstructive nephropathy [77], and CKD [78].

$H_2S$ regulates basic physiologic mechanisms of the kidney such as sodium reabsorption, glomerular filtration, and renal homeostasis [17]. In some animal models of kidney disease, such as CKD [79], acute kidney injury [80], cisplatin nephropathy [81], obstructive

nephropathy [82], and diabetic nephropathy [83], it can serve as an agent that ameliorates kidney injury.

### 3.3. Crosstalk between NO, CO, and H₂S in the Kidney and BP Control

Although NO and $H_2S$ share the same sGC–cGMP pathway to elicit relaxation in kidney cells [16], they act at different levels, with NO increasing production of cGMP through stimulation of sGC and $H_2S$ inhibiting cGMP degradation [84]. In rats, inhibition of NO by L-NAME, causes hypertension that can be prevented by the administration of sodium hydrosulfide (NaHS, a $H_2S$ donor), which also rescues NO bioavailability [85]. These data support the notion that there exists a NO/$H_2S$ crosstalk in the control of blood pressure (BP).

One of the NO-based cellular signaling pathways is via protein S-nitrosylation, the covalent addition of NO moiety to the sulfur atom of cysteine residues [86]. S-nitrosylation of specific proteins has been shown to be protective against kidney injury [86]. As observed for NO, $H_2S$ also employs post-translational modifications, namely, S-sulfhydration [87]. Endogenous $H_2S$ physiologically S-sulfydrates proteins on the thiol group of cysteine residues (e.g., glutathione), leading to the formation of the –SSH moiety. These observations lead to a hypothesis that there might be competition between S-nitrosylation and S-sulfhydration for the same cysteine residues in proteins, thus allowing the two gasotransmitters to regulate each other [84].

CO could also target sGC and regulate NO-mediated vasodilatation [88], which was supported by a report showing that transgenic mice overexpressing cell-specific HO-1 exhibit hypertension coinciding with decreased cGMP production in response to NO [89]. Additionally, CO could interfere with NOS activity and reduce NO generation as a consequence, thereby limiting NO-mediated vasodilation [90]. Although much is known about the CO and NO signaling pathways in the kidney, we so far do not fully understand how these two gaseous signaling systems interact with each other.

Moreover, all three gasotransmitters are involved in activation of nuclear factor erythroid 2-related factor 2 (NRF2) (Figure 2). NRF2 is a major regulator of HO-1 transcription responding to oxidative stress [72]. Upon activation, the NRF2-HO-1 pathway protects chronic kidney disease progression related to reduction of oxidative stress, inhibition of transforming growth factor-β (TGF-β)-driven fibrosis, reduction of inflammation and apoptosis [91]. Under basal conditions, NRF2 levels are kept low through the interaction with Kelch-like ECH associated protein 1 (KEAP1). Upon binding, the NRF2-KEAP1 interaction stabilizes the complex allowing for ubiquitylation, and ultimately proteasomal degradation of NRF2 [91]. Of note, NO and $H_2S$ can activate NRF2 via S-nitrosylation and S-sulfhydration of KEAP1, respectively [92,93]. In addition to NRF2, NO can regulate other redox-regulatory transcription factors, like nuclear factor κB (NFκB) and hypoxia-inducible factor-1α (HIF-1α), via S-nitrosylation [92]. As NFκB mediates inflammation and HIF-1α induces HO-1 expression, NO can interact with the NRF2–HO-1–CO signaling pathway in many different ways to prevent CKD progression. NFκB can also be S-sulfhydrated by $H_2S$ [93]. These observations indicate crosstalk mechanisms between NO, CO, and $H_2S$ are important determinants for kidney disease (Figure 2).

Although the beneficial actions of gasotransmitters against established kidney disease and hypertension have been established, their roles in mediating programmed responses behind developmental origins remain unclear. For this reason, this review will next outline the potential early-life interventions targeting NO, CO, and $H_2S$ signaling that may pose new opportunities for the therapeutic protection of hypertension and kidney disease.
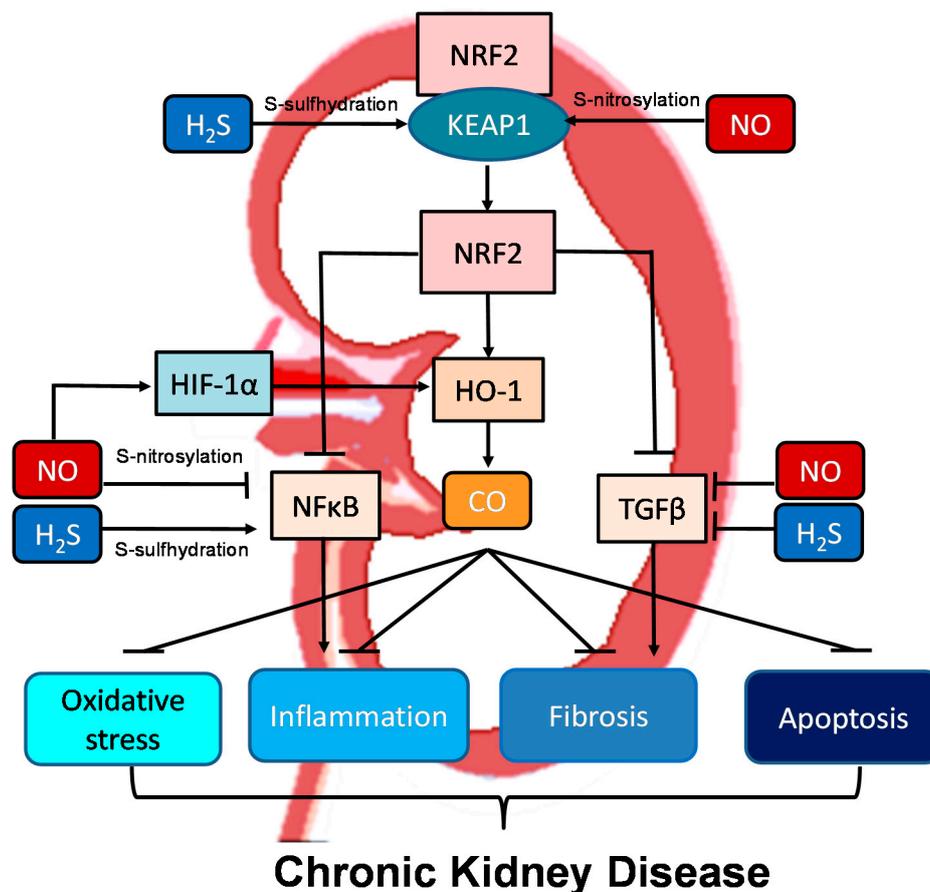
**Figure 2.** Schematic illustration of the crosstalk among NO, CO, and H$_2$S and downstream nuclear factor erythroid 2-related factor 2 (NRF2)–heme oxygenase-1 (HO-1) signaling able to protect chronic kidney disease progression. Activation of the NRF2–HO-1–CO signaling pathway suppresses nuclear factor κB (NFκB) and transforming growth factor-β (TGF-β), consequently inhibiting oxidative stress, inflammation, fibrosis, and apoptosis. NO and H$_2$S can activate NRF2 via S-nitrosylation and S-sulfhydration of Kelch-like ECH associated protein 1 (KEAP1), respectively. Via S-nitrosylation, NO can also inhibit NFκB-induced inflammation and activate hypoxia-inducible factor-1α (HIF-1α), a HO-1 inducer. Additionally, NFκB can also be regulated by H$_2$S via S-sulfhydration. NO and H$_2$S also reduce TGFβ-mediated fibrosis.

## 4. Developmental Origins of Hypertension and Kidney Disease

### 4.1. Animal Models of Gasotransmitter-Related Renal Programming

So far, little reliable information exists regarding the impact of gasotransmitters on the development of hypertension and kidney disease in humans. Animal models enable researchers to consider various adverse environmental conditions in developmental stages to determine underlying programming processes and long-term outcome in adult offspring.

The developing kidney is extremely vulnerable to the effects of adverse environmental events, resulting in renal programming and eventually functional alterations and structural changes [94]. As reviewed elsewhere [10,12,21,94,95], renal programming is the major determinant of hypertension and kidney disease of developmental origins. Animal models particularly have provided more direct insight into the association between NO, CO, H$_2$S, and renal programming. The current review is solely restricted to early-life insults starting in pregnancy and lactation period with focusing on gasotransmitter-related renal programming. Table 2 illustrates a variety of adverse conditions during pregnancy and lactation which may affect kidney development, resulting in hypertension and adverse renal outcomes in adulthood [71,96–108].

**Table 2.** Summary of animal models of renal programming related to NO, CO, and H₂S signaling.

| Animal Models | Species/ Gender | Age at Evaluation | Mechanisms Related to Gasotransmitter | Renal Outcome and Blood Pressure | Ref. |
|---|---|---|---|---|---|
| **Nitric oxide (NO)** | | | | | |
| Maternal caloric restriction diet | SD rats/M | 12 weeks | ↑ ADMA ↓NO | Glomerular hypertrophy, ↑Tubulointerstitial injury and BP ↓Nephron number | [96,97] |
| Streptozotocin-induced diabetes | SD rats/M | 12 weeks | ↑ADMA ↓NO | ↑Tubulointerstitial injury and BP ↓Nephron number | [98] |
| Maternal suramin administration | SD rats/M | 12 weeks | ↑ADMA ↓NO | ↑BP | [99] |
| Maternal high-fructose diet | SD rats/M | 12 weeks | ↓NO | ↑BP | [100] |
| Maternal adenine-induced CKD | SD rats/M | 12 weeks | ↑ADMA ↓NO | Renal hypertrophy ↑BP | [101] |
| Prenatal dexamethasone exposure | SD rats/M | 16 weeks | ↓Renal NO | ↑BP | [102] |
| Prenatal dexamethasone exposure plus postnatal high-fat intake | SD rats/M | 16 weeks | ↓NO | ↑BP | [103] |
| Prenatal dexamethasone plus TCDD exposure | SD rats/M | 16 weeks | ↑ADMA | ↑BP | [104] |
| Prenatal bisphenol A exposure plus high-fat diet | SD rats/M | 16 weeks | ↑ADMA ↓NO | ↑BP | [105] |
| Prenatal betamethasone exposure | Sheep/M and F | 18 months | ↓NO | ↑BP | [71] |
| **Carbon monoxide (CO)** | | | | | |
| Streptozotocin-induced diabetes | Hoxb7-GFP-Tg mice/M | 20 weeks | ↑Renal HO-1 expression | Proteinuria, ↑Kidney injury, ↓GFR, ↑BP | [106] |
| **Hydrogen sulfide (H₂S)** | | | | | |
| Maternal suramin administration | SD rats/M | 12 weeks | ↓Renal H₂S releasing activity | ↑BP | [99] |
| Maternal hypertension | SHRs/M | 12 weeks | ↓Renal 3MST protein expression & renal H₂S releasing activity | ↑BP | [107] |
| Prenatal dexamethasone exposure plus postnatal high-fat intake | SD rats/M | 16 weeks | ↓Renal CBS and 3MST protein expression | ↑BP | [103] |
| Maternal and post-weaning high-fat diet | SD rats/M | 16 weeks | ↓Plasma H₂S level | ↑BP | [108] |

Studies tabulated according to types of gasotransmitters, species, and age at evaluation. TCDD = 2,3,7,8-tetrachlorodibenzo-p-dioxin; CKD = Chronic kidney disease; ADMA = asymmetric dimethylarginine; SD = Sprague Dawley; SHR = spontaneously hypertensive rat; M = male; F = female; GFR = glomerular filtration rate; ↑ = increased; ↓ = decreased.

As shown in Table 2, the most common phenotype of renal programming being studied is hypertension [71,96–108]. Reduced nephron number has been demonstrated in offspring rats born of dams with caloric restriction [96,97] or streptozotocin-induced diabetes [98].

Our previous study reported that ADMA (a reactive oxygen species (ROS) inducer and endogenous NOS inhibitor) impaired ureteric bud branching morphogenesis, consequently leading to decreases of nephron number [32]. Additionally, kidney injury was addressed in models of maternal caloric restriction [96,97] and streptozotocin-induced diabetes [98,106]. Renal function was not determined or unaltered in most models of renal programming. In one study, GFR was decreased in 20-week-old mice offspring born to dams developed streptozotocin-induced diabetes [106]. Our review implicates that various early-life insults are relevant to renal programming, including maternal nutritional imbalance [96,97,100,108], maternal illnesses [98,99,101,106], prenatal environmental chemical exposures [104,105], and medication use during pregnancy [102–104].

Most studies focused on gasotransmitter NO [71,96–105], followed by H₂S [99,103,107,108] and CO [106]. Impaired ADMA–NO pathway was reported in several models of renal

programming, including maternal caloric restriction [96,97], streptozotocin-induced diabetes [98], maternal suramin administration [99], high-fructose diet [100], maternal adenine-induced CKD [101], prenatal glucocorticoid exposure [71,102], prenatal dexamethasone plus high-fat diet [103], prenatal dexamethasone plus TCDD exposure [104], and combined bisphenol A and high-fat diet exposure [105].

However, there is only one report demonstrating HO-1 is involved in maternal diabetes-induced hypertension and kidney disease [106]. Moreover, reduced renal $H_2S$-synthesing enzyme expression, decreased renal $H_2S$ releasing activity, and low plasma $H_2S$ level have been reported in various models of programmed hypertension [99,103,107,108].

### 4.2. Therapeutic Prevention of Gasotransmitters for Hypertension and Kidney Disease of Developmental Origins

Various early-life insults can cause similar renal phenotypes, implying the existence of common pathways behind renal programming that may contribute to hypertension and kidney disease of developmental origins. Although the pathogenetic mechanisms have not yet been fully disclosed, certain renal programming mechanisms have been documented, including but not limited to, oxidative stress, aberrant renin–angiotensin system (RAS), dysregulated nutrient sensing signals, epigenetic regulation, gut microbiota dysbiosis, and sex differences [10,12,13,18,20–22,109–111]. Of note, each of the three gas signaling molecules has approximately mutual relationships with the above-mentioned mechanisms.

With a greater understanding of mechanisms behind renal programming, implementation of interventions for therapeutic prevention of hypertension and kidney disease in later life is feasible. An important message is that whereas therapeutic interventions can be delivered at any disease stage, reprogramming is barely restricted to key periods during early development. Here, we summarize the knowledge available today regarding gasotransmitters used as reprogramming strategies for developmental hypertension and kidney disease in various animal models [39,40,96,98,99,102–104,108,112–121], all of which are documented in Table 3. This review is only limited to gasotransmitter-based interventions as reprogramming strategies applied during pregnancy and/or lactation which are critical periods for kidney development.

**Table 3.** Summary of gasotransmitter-based interventions used for therapeutic prevention of hypertension and kidney disease of developmental origins.

| Gasotransmitter-Based Intervention | Animal Models | Species/ Gender | Age at Evaluation | Therapeutic Effects | Ref. |
|---|---|---|---|---|---|
| **Nitric oxide (NO)** | | | | | |
| Substrate for NOS | | | | | |
| 0.25% L-Citrulline in drinking water during pregnancy and lactation | Maternal L-NAME exposure | SD rats/M | 12 weeks | Prevented hypertension | [40] |
| 0.25% L-Citrulline in drinking water during pregnancy and lactation | Maternal caloric restriction | SD rats/M | 12 weeks | Prevented kidney damage, increased nephron number | [96] |
| 0.25% L-Citrulline in drinking water during pregnancy and lactation | Streptozotocin-induced diabetes | SD rats/M | 12 weeks | Prevented hypertension and kidney damage, increased nephron number | [98] |
| 0.25% L-Citrulline in drinking water during pregnancy and lactation | Prenatal dexamethasone exposure | SD rats/M | 12 weeks | Prevented hypertension, increased nephron number | [102] |
| L-Citrulline (2.5 g/L) in drinking water from 2 weeks before until 6 weeks after birth | Genetic hypertension model | SHR/M & F | 50 weeks | Prevented hypertension | [112] |

**Table 3.** *Cont.*

| Gasotransmitter-Based Intervention | Animal Models | Species/ Gender | Age at Evaluation | Therapeutic Effects | Ref. |
|---|---|---|---|---|---|
| NO donors | | | | | |
| Pentaerythritol tetranitrate (50 mg/kg per day) during pregnancy and lactation | Genetic hypertension model | SHR/M & F | 8 months | Prevented hypertension | [113] |
| Molsidomine (120 mg/L in drinking water) from 2 weeks before until 4 weeks after birth | Genetic hypertension model | FHH/M & F | 42 weeks | Prevented hypertension | [114] |
| Asymmetric dimethylarginine (ADMA)-lowering agents | | | | | |
| Resveratrol (50mg/L in drinking water) during pregnancy and lactation | Prenatal dexamethasone plus TCDD exposure | SD rats/M | 12 weeks | Prevented hypertension | [104] |
| Melatonin (0.01% in drinking water) during pregnancy and lactation | Maternal high-fructose diet plus post-weaning high-salt diet | SD rats/M | 12 weeks | Prevented hypertension | [115] |
| Aliskiren (10 mg/kg/day) from 2 weeks to 4 weeks after birth | Maternal caloric restriction | SD rats/M | 12 weeks | Prevented hypertension | [116] |
| NAC (1% in drinking water) during pregnancy and lactation | Prenatal dexamethasone exposure plus postnatal high-fat intake | SD rats/M | 16 weeks | Prevented hypertension | [103] |
| Enhancement of NOS | | | | | |
| Melinjo (Gnetum gnemon) seed extract (1% in diet) from birth to postnatal week 3 | Maternal high-fructose diet | Wistar rats/F | 16 weeks | Prevented hypertension | [117] |
| **Carbon monoxide(CO)** | | | | | |
| NRF2 activator | | | | | |
| Daily oral gavage of dimethyl fumarate (50mg/kg/day) for 3 weeks during pregnancy | Prenatal dexamethasone exposure plus postnatal high-fat intake | SD rats/M & F | 16 weeks | Prevented hypertension | [118] |
| **Hydrogen sulfide (H$_2$S)** | | | | | |
| H$_2$S donors | | | | | |
| Daily intraperitoneal injection of NaHS (56 μmol/kg/day) during pregnancy and lactation | 2-kidney, 1-clip renovascular hypertension model | SD rats/M & F | 16 weeks | Prevented hypertension | [119] |
| Precursors of H$_2$S | | | | | |
| NAC (1% in drinking water) during pregnancy and lactation | Maternal L-NAME exposure | SD rats/M | 12 weeks | Prevented hypertension | [39] |
| NAC (1% in drinking water) during pregnancy and lactation | Suramin administration | SD rats/M | 12 weeks | Prevented hypertension | [99] |
| NAC (1% in drinking water) during pregnancy and lactation | Prenatal dexamethasone and postnatal high-fat diet | SD rats/M | 12 weeks | Prevented hypertension | [103] |
| NAC (1% in drinking water) during pregnancy and lactation | Maternal hypertension | SHRs/M | 12 weeks | Prevented hypertension | [108] |
| NAC (500 mg/kg/day) in drinking water from gestational day 4 to postnatal day 10 | Maternal nicotine exposure | SD rats/M | 8 months | Prevented hypertension | [120, 121] |
| Organosulfur compounds | | | | | |
| Daily oral gavage of garlic oil (100 mg/kg/day) during pregnancy and lactation | Maternal and postweaning high-fat diet | SD rats/M | 16 weeks | Prevented hypertension | [107] |

Studies tabulated according to types of gasotransmitters and modalities, animal models and age at evaluation. L−NAME = N$^G$-nitro-L-arginine-methyl ester. M = male. F = female. NAC = N-acetylcysteine. NaHS = sodium hydrosulfide. SHR = spontaneously hypertensive rat. SD = Sprague−Dawley rat. FHH = Fawn hooded hypertensive rat.

Evidence from the studies reviewed indicates that rats are the most commonly used animal models. Rats become sexually mature at 6 weeks. In adulthood, one rat month is comparable to three human years [122]. Accordingly, Table 3 lists the therapeutic effects

determined in rats ranging from 12 weeks to 8 months of rat age, which allows calculations to extract data for the specific age group that can be translated to humans. Note that little information currently exists in regard to large animals used for studying the roles of gasotransmitters on hypertension and kidney disease of developmental origins.

### 4.3. Nitric Oxide

Several therapeutic interventions have been used to increase NO bioavailability, such as supplementation of NO substrate, NO donors, ADMA-lowering agents, and enhancement of the expression and/or activity of NOS [18]. Nevertheless, only some of them have been reported for therapeutic prevention of programmed kidney disease and hypertension (Table 3).

L-Arginine supplementation has been considered as a therapeutic approach to improve NO bioavailability in human diseases [123], whereas its benefits from human trials remain inconclusive [124]. Although perinatal arginine supplementation combined with antioxidants has been reported to protect adult offspring against hypertension in spontaneously hypertensive rats (SHRs) and Fawn-hooded hypertensive (FHH) rats [125,126], whether perinatal arginine supplementation alone is able to reprogram hypertension and kidney disease of developmental origins has not been elucidated yet.

Because L-Citrulline can be converted to L-Arginine and it can bypass hepatic metabolism, oral L-Citrulline supplementation has been used as an add-on therapy to increase L-Arginine concentrations, subsequently increasing NO production [127]. Table 3 illustrates several models have been used to examine the reprogramming effects of perinatal L-Citrulline supplementation, including maternal $N^G$-nitro–L-arginine methyl ester (L-NAME) exposure [40], maternal caloric restriction [96], streptozotocin-induced diabetes [98], and prenatal dexamethasone exposure [102]. In addition, early supplementation with L-Citrulline in young SHRs prevents the transition from prehypertension to hypertension [112].

The use of NO donors is another way to increase NO. Two NO donors—pentaerythritol tetranitrate and molsidomine—have been reported to prevent the development of hypertension in SHRs and FFH rats, respectively [113,114] (Table 3). However, so far little information exists with regard to NO donors in programming models to prevent kidney disease of developmental origins. Currently, a specific ADMA-lowering agent remains inaccessible. However, many currently used drugs have been reported to lower ADMA levels and restore NO bioavailability in human and experimental studies [14,19,106]. Among them—rosuvastatin, telmisartan, glucagon-like peptide-1 receptor agonist, and epigallocatechin-3-gallate—can decrease PRMT-1 (ADMA-generating enzyme) expression to reduce ADMA levels. Furthermore, telmisartan, resveratrol, metformin, melatonin, atorvastatin, N-acetylcysteine (NAC), vitamin E, salvianolic acid A, oxymatrine, and rosuvastatin have been reported to reduce ADMA level via enhancing the activity and/or expression of DDAHs (ADMA-metabolizing enzymes) [14]. Table 3 shows only few ADMA-lowering agents have been examined in the developmental programming models to prevent hypertension, including NAC [103], resveratrol [104], melatonin [115], and aliskiren [116]. Moreover, in mother rats that received melinjo (Gnetum gnemon) seed extract during lactation the development of hypertension programmed by excessive fructose intake in their female offspring could be prevented by enhancing eNOS expression [117].

### 4.4. Carbon Monoxide

As opposed to NO, limited information is available about the CO-based interventions to study their roles on kidney disease and hypertension of developmental origins. Carbon monoxide releasing molecules (CORMs), a group of chemical compounds capable of controlled CO release directly in tissues or organs, have emerged as a therapeutic tool for human diseases [128]. However, none of them have been examined in kidney disease and hypertension of developmental origins.

In addition to CORMs, HO-1 or Nrf2 activators are potential CO-based modalities to activate the NRF2–HO-1–CO signaling pathway. Many natural compounds have shown to be effective activators of NRF2/HO-1 like resveratrol, curcumin, quercetin, anthocyanins, carnosic acid, epigallocatechin gallate, celastrol, isothiocyanates, garlic-derived organosulfur compounds, etc. [129]. Aside from natural activators, some synthetic NRF2 activators have been developed for clinical application like dimethyl fumarate (DMF), oltipraz, and ursodiol [130].

There is general lack of studies investigating NRF2/HO-1 activators for the prevention of kidney disease of developmental origins. As shown in Table 3, only one study reported that maternal DMF treatment protected adult progeny against hypertension in a maternal dexamethasone exposure and postnatal high-fat diet model [118]. Our previous study demonstrated resveratrol therapy during pregnancy and lactation protects adult offspring against bisphenol A-induced liver damage is associated with activation of NRF2 [131]. Nevertheless, the impact of early-life resveratrol supplementation on NRF2/HO-1/CO signaling pathway awaits further elucidation.

### 4.5. Hydrogen Sulfide

So far, available $H_2S$-based modalities used for therapeutic protection of hypertension and kidney disease include $H_2S$ donors, precursors of $H_2S$, and organosulfur compounds. Inorganic sulfide salts like sodium hydrosulfide (NaHS) are the most widely used $H_2S$ donors to evaluate the therapeutic potential of exogenous $H_2S$ [68]. NaHS has shown anti-hypertensive effects in several hypertensive models, including NO-deficient rats [62], Dahl salt-sensitive rats [63], and SHRs [132]. In line with established hypertensive models, Table 3 shows maternal NaHS therapy during pregnancy and lactation periods prevented hypertension in adult offspring born to dams with renovascular hypertension [119]. Nevertheless, other $H_2S$ donors have not yet been tested in terms of their reprogramming effects on hypertension and kidney disease of developmental origins.

Precursors of $H_2S$ include L-Cysteine, D-Cysteine, and NAC, a stable cysteine analog. Table 3 shows perinatal NAC therapy protects adult offspring against hypertension programmed by various early-life insults, such as maternal L-NAME exposure [39], maternal suramin administration [99], prenatal dexamethasone and postnatal high-fat diet [103], maternal hypertension [108], and maternal nicotine exposure [120,121]. Although D- or L-cysteine supplementation between four and six weeks of age has been found to protect high salt-treated SHRs against hypertension and kidney injury at 12 weeks old [133], their uses in pregnancy and lactation implicating programming hypertension and kidney disease has not been explored yet. Another report demonstrated that supplementing garlic oil in pregnancy and lactation prevented hypertension programmed by a high-fat diet, which coinciding with increased expression and activity of $H_2S$-producing enzymes in offspring kidneys [107]. Organosulfur compounds derived from garlic are natural precursors of $H_2S$ [134].

Several clinically used medications have been shown to increase $H_2S$ concentrations, such as amlodipine, aspirin, carvediol, atorvastatin, digoxin, paracetamol, metformin, ramipril, testosterone, vitamin D, and 17β-estradiol [135]. Additionally, significant progress has been achieved in recent years on new $H_2S$-releasing drugs. It would be interesting to see whether these $H_2S$-releasing drugs would appear to be a practical approach to prevent hypertension and kidney disease from further clinical translation.

Collectively, these findings indicate the potential impact of gasotransmitter-based interventions for therapeutic prevention of programmed kidney disease and hypertension. While these studies have also raised concern, the protective mechanisms behind some gasotransmitter-based interventions are not limited to only one gasotransmitter. For example, resveratrol has properties to lower ADMA and activate NRF2; however, to what extent its reprogramming effects on kidney disease and hypertension can be attributed to NO or CO deserves further clarification. Accordingly, a better understanding of each

gasotransmitter-dependent and -independent mechanisms responsible for the reprogramming effects of various gasotransmitter-based interventions is therefore highly warranted.

## 5. Conclusions and Future Perspectives

Current evidences suggest a potential therapeutic role of gasotransmitter-based interventions for prevention of programmed hypertension and kidney disease. Although many NO-, CO-, and H2S-based drugs have led to a significant progress in our understanding of established hypertension and kidney disease, attention must be paid to prevent (and not just to treat) these diseases; translation from animal models into clinical practice will be an additional challenge.

Of note, much of the preclinical work investigated the reprogramming actions of NO and H2S, and most of them focused on hypertension of developmental origins. Nevertheless, there is little reliable information about the reprogramming effects of CO-based intervention. Meanwhile, we are aware that almost no studies have taken a holistic approach to simultaneous determinations of NO, CO, and H2S signaling pathway in one experiment. In view of the complex interplay between these three gasotransmitters, the reprogramming effect responding to each gasotransmitter-based intervention, either individually or in combination, are incomplete and difficult to predict. Furthermore, more attention should be paid to decide the optimal dosage and duration of gasotransmitter-based intervention using the appropriate animal models prior to clinical translation.

## References

1. Kajimura, M.; Fukuda, R.; Bateman, R.M.; Yamamoto, T.; Suematsu, M. Interactions of multiple gas-transducing systems: Hallmarks and uncertainties of CO, NO, and H2S gas biology. *Antioxid. Redox Signal.* **2010**, *13*, 157–192. [CrossRef] [PubMed]
2. Polhemus, D.J.; Lefer, D.J. Emergence of hydrogen sulfide as an endogenous gaseous signaling molecule in cardiovascular disease. *Circ. Res.* **2014**, *114*, 730–737. [CrossRef] [PubMed]
3. NIOSH Pocket Guide to Chemical Hazards. 2020. Available online: https://www.cdc.gov/niosh/npg/ (accessed on 19 July 2021).
4. Lancaster, J.R. Historical origins of the discovery of mammalian nitric oxide (nitrogen monoxide) production/physiology/ pathophysiology. *Biochem. Pharmacol.* **2020**, *176*, 113793. [CrossRef] [PubMed]
5. Durante, W. Carbon monoxide and bile pigments: Surprising mediators of vascular function. *Vasc. Med.* **2002**, *7*, 195–202. [CrossRef]
6. Kimura, H. The physiological role of hydrogen sulfide and beyond. *Nitric Oxide* **2014**, *41*, 4–10. [CrossRef]
7. World Health Organization. Hypertension. 2019. Available online: https://www.who.int/news-room/fact-sheets/detail/ hypertension (accessed on 12 May 2021).
8. Lozano, R.; Naghavi, M.; Foreman, K.; Lim, S.; Shibuya, K.; Aboyans, V.; Abraham, J.; Adair, T.; Aggarwal, R.; Ahn, S.Y.; et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet* **2012**, *380*, 2095–2128. [CrossRef]
9. Weir, M.R. Hypertension and the kidney: Perspectives on the relationship of kidney disease and cardiovascular disease. *Clin. J. Am. Soc. Nephrol.* **2009**, *4*, 2045–2050. [CrossRef]
10. Tain, Y.L.; Hsu, C.N. Developmental origins of chronic kidney disease: Should we focus on early life? *Int. J. Mol. Sci.* **2017**, *18*, 381. [CrossRef]
11. Haugen, A.C.; Schug, T.T.; Collman, G.; Heindel, J.J. Evolution of DOHaD: The impact of environmental health sciences. *J. Dev. Orig. Health Dis.* **2015**, *6*, 55–64. [CrossRef] [PubMed]

12. Tain, Y.L.; Joles, J.A. Reprogramming: A preventive strategy in hypertension focusing on the kidney. *Int. J. Mol. Sci.* **2016**, *17*, 23. [CrossRef]

13. Paauw, N.D.; van Rijn, B.B.; Lely, A.T.; Joles, J.A. Pregnancy as a critical window for blood pressure regulation in mother and child: Programming and reprogramming. *Acta Physiol.* **2017**, *219*, 241–259. [CrossRef] [PubMed]

14. Baylis, C. Nitric oxide synthase derangements and hypertension in kidney disease. *Curr. Opin. Nephrol. Hypertens.* **2012**, *21*, 1–6. [CrossRef] [PubMed]

15. Csongradi, E.; Juncos, L.A.; Drummond, H.A.; Vera, T.; Stec, D.E. Role of carbon monoxide in kidney function: Is a little carbon monoxide good for the kidney? *Curr. Pharm. Biotechnol.* **2012**, *13*, 819–826. [CrossRef] [PubMed]

16. Feliers, D.; Lee, H.J.; Kasinath, B.S. Hydrogen sulfide in renal physiology and disease. *Antioxid. Redox Signal.* **2016**, *25*, 720–731. [CrossRef]

17. Scammahorn, J.J.; Nguyen, I.T.N.; Bos, E.M.; Van Goor, H.; Joles, J.A. Fighting oxidative stress with sulfur: Hydrogen sulfide in the renal and cardiovascular systems. *Antioxidants* **2021**, *10*, 373. [CrossRef]

18. Hsu, C.N.; Tain, Y.L. Regulation of nitric oxide production in the developmental programming of hypertension and kidney disease. *Int. J. Mol. Sci.* **2019**, *20*, 681. [CrossRef]

19. Hsu, C.N.; Tain, Y.L. Preventing developmental origins of cardiovascular disease: Hydrogen sulfide as a potential target? *Antioxidants* **2021**, *10*, 247. [CrossRef]

20. Chong, E.; Yosypiv, I.V. Developmental programming of hypertension and kidney disease. *Int. J. Nephrol.* **2012**, *2012*, 760580. [CrossRef]

21. Paixão, A.D.; Alexander, B.T. How the kidney is impacted by the perinatal maternal environment to develop hypertension. *Biol. Reprod.* **2013**, *89*, 144. [CrossRef]

22. Hsu, C.N.; Tain, Y.L. Animal models for DOHaD research: Focus on hypertension of developmental origins. *Biomedicines* **2021**, *9*, 623. [CrossRef]

23. Holwerda, K.M.; Faas, M.M.; van Goor, H.; Lely, A.T. Gasotransmitters: A solution for the therapeutic dilemma in preeclampsia? *Hypertension* **2013**, *62*, 653–659. [CrossRef] [PubMed]

24. Guerra, D.D.; Hurt, K.J. Gasotransmitters in pregnancy: From conception to uterine involution. *Biol. Reprod.* **2019**, *101*, 4–25. [CrossRef] [PubMed]

25. Rengarajan, A.; Mauro, A.K.; Boeldt, D.S. Maternal disease and gasotransmitters. *Nitric Oxide* **2020**, *96*, 1–12. [CrossRef]

26. Rosselli, M.; Keller, P.J.; Dubey, R.K. Role of nitric oxide in the biology, physiology and pathophysiology of reproduction. *Hum. Reprod. Update* **1998**, *4*, 3–24. [CrossRef] [PubMed]

27. Lundberg, J.O.; Weitzberg, E.; Gladwin, M.T. The nitrate-nitrite-nitric oxide pathway in physiology and therapeutics. *Nat. Rev. Drug Discov.* **2008**, *7*, 156–167. [CrossRef]

28. Chin-Dusting, J.P.; Willems, L.; Kaye, D.M. L-Arginine transporters in cardiovascular disease: A novel therapeutic target. *Pharmacol. Ther.* **2007**, *116*, 428–436. [CrossRef]

29. Tain, Y.L.; Hsu, C.N. Toxic Dimethylarginines: Asymmetric Dimethylarginine (ADMA) and Symmetric Dimethylarginine (SDMA). *Toxins* **2017**, *9*, 92. [CrossRef] [PubMed]

30. Leiper, J.; Vallance, P. Biological significance of endogenous methylarginines that inhibit nitric oxide synthases. *Cardiovasc. Res.* **1999**, *43*, 542–548. [CrossRef]

31. Hsu, C.N.; Tain, Y.L. Impact of arginine nutrition and metabolism during pregnancy on offspring outcomes. *Nutrients* **2019**, *11*, 1452. [CrossRef] [PubMed]

32. Sand, A.; Andersson, E.; Fried, G. Nitric oxide donors mediate vasodilation in human placental arteries partly through a direct effect on potassium channels. *Placenta* **2006**, *27*, 181–190. [CrossRef] [PubMed]

33. Bavoux, F.; Georges, P.; Bouy, M.; Leroy, B. Growth retardation and amino acids. Analysis of maternal plasma and amniotic fluid. *J. Gynecol. Obstet. Biol. Reprod.* **1977**, *6*, 931–940.

34. Kim, Y.J.; Park, H.S.; Lee, H.Y.; Ha, E.H.; Suh, S.H.; Oh, S.K.; Yoo, H.S. Reduced L-arginine level and decreased placental eNOS activity in preeclampsia. *Placenta* **2006**, *27*, 438–444. [CrossRef]

35. Pettersson, A.; Hedner, T.; Milsom, I. Increased circulating concentrations of asymmetric dimethyl arginine (ADMA), an endogenous inhibitor of nitric oxide synthesis, in preeclampsia. *Acta Obstet. Gynecol. Scand.* **1998**, *77*, 808–813. [PubMed]

36. Leiva, A.; Fuenzalida, B.; Barros, E.; Sobrevia, B.; Salsoso, R.; Sáez, T.; Villalobos, R.; Silva, L.; Chiarello, I.; Toledo, F.; et al. Nitric oxide is a central common metabolite in vascular dysfunction associated with diseases of human pregnancy. *Curr. Vasc. Pharmacol.* **2016**, *14*, 237–259. [CrossRef] [PubMed]

37. Abraham, A.J.M.; Bobby, Z.; Chaturvedula, L.; Vinayagam, V.; Syed, H.; Jacob, S.E. Utility of time of onset of hypertension, ADMA and TAS in predicting adverse neonatal outcome in hypertensive disorders of pregnancy. *Fetal Pediatr. Pathol.* **2019**, *38*, 460–476. [CrossRef] [PubMed]

38. Kusinski, L.C.; Stanley, J.L.; Dilworth, M.R.; Hirt, C.J.; Andersson, I.J.; Renshall, L.J.; Baker, B.C.; Baker, P.N.; Sibley, C.P.; Wareing, M.; et al. eNOS knockout mouse as a model of fetal growth restriction with an impaired uterine artery function and placental transport phenotype. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2012**, *303*, R86–R93. [CrossRef] [PubMed]

39. Tain, Y.L.; Lee, C.T.; Chan, J.Y.; Hsu, C.N. Maternal melatonin or N-acetylcysteine therapy regulates hydrogen sulfide-generating pathway and renal transcriptome to prevent prenatal NG-Nitro-L-arginine-methyl ester (L-NAME)-induced fetal programming of hypertension in adult male offspring. *Am. J. Obstet. Gynecol.* **2016**, *215*, 636.e1–636.e72. [CrossRef]

40. Tain, Y.L.; Huang, L.T.; Lee, C.T.; Chan, J.Y.; Hsu, C.N. Maternal citrulline supplementation prevents prenatal N$^{G}$-nitro-l-arginine-methyl ester (L-NAME)-induced programmed hypertension in rats. *Biol. Reprod.* **2015**, *92*, 7. [CrossRef]

41. Hartsfield, C.L. Cross talk between carbon monoxide and nitric oxide. *Antioxid. Redox Signal.* **2002**, *4*, 301–307. [CrossRef] [PubMed]

42. Sharma, V.S.; Magde, D. Activation of soluble guanylate cyclase by carbon monoxide and nitric oxide: A mechanistic model. *Methods* **1999**, *19*, 494–505. [CrossRef]

43. Kreiser, D.; Baum, M.; Seidman, D.S.; Fanaroff, A.; Shah, D.; Hendler, I.; Stevenson, D.K.; Schiff, E.; Druzin, M.L. End tidal carbon monoxide levels are lower in women with gestational hypertension and pre-eclampsia. *J. Perinatol.* **2004**, *24*, 213–217. [CrossRef]

44. Bainbridge, S.A.; Farley, A.E.; McLaughlin, B.E.; Graham, C.H.; Marks, G.S.; Nakatsu, K.; Brien, J.F.; Smith, G.N. Carbon monoxide decreases perfusion pressure in isolated human placenta. *Placenta* **2002**, *23*, 563–569. [CrossRef]

45. Zhao, H.; Wong, R.J.; Kalish, F.S.; Nayak, N.R.; Stevenson, D.K. Effect of heme oxygenase-1 deficiency on placental development. *Placenta* **2009**, *30*, 861–868. [CrossRef]

46. Patel, P.; Vatish, M.; Heptinstall, J.; Wang, R.; Carson, R.J. The endogenous production of hydrogen sulphide in intrauterine tissues. *Reprod. Biol. Endocrinol.* **2009**, *7*, 10. [CrossRef]

47. Shibuya, N.; Kimura, H. Production of hydrogen sulfide from d-cysteine and its therapeutic potential. *Front. Endocrinol.* **2013**, *4*, 87. [CrossRef]

48. Linden, D.R. Hydrogen Sulfide Signaling in the Gastrointestinal Tract. *Antioxid. Redox Signal.* **2014**, *20*, 818–830. [CrossRef] [PubMed]

49. Lorca, R.A.; Prabagaran, M.; England, S.K. Functional insights into modulation of BKCa channel activity to alter myometrial contractility. *Front. Physiol.* **2014**, *5*, 289. [CrossRef]

50. Benkusky, N.A.; Fergus, D.J.; Zucchero, T.M.; England, S.K. Regulation of the Ca2+-sensitive domains of the maxi-K channel in the mouse myometrium during gestation. *J. Biol. Chem.* **2000**, *275*, 27712–27719. [CrossRef] [PubMed]

51. Cindrova-Davies, T.; Herrera, E.A.; Niu, Y.; Kingdom, J.; Giussani, D.A.; Burton, G.J. Reduced cystathionine γ-lyase and increased miR-21 expression are associated with increased vascular resistance in growth-restricted pregnancies: Hydrogen sulfide as a placental vasodilator. *Am. J. Pathol.* **2013**, *182*, 1448–1458. [CrossRef] [PubMed]

52. Sheibani, L.; Lechuga, T.J.; Zhang, H.; Hameed, A.; Wing, D.A.; Kumar, S.; Rosenfeld, C.R.; Chen, D.B. Augmented H2S production via cystathionine beta-synthase upregulation plays a role in pregnancy-associated uterine vasodilation. *Biol. Reprod.* **2017**, *96*, 664–672. [CrossRef]

53. Wang, K.; Ahmad, S.; Cai, M.; Rennie, J.; Fujisawa, T.; Crispi, F.; Baily, J.; Miller, M.R.; Cudmore, M.; Hadoke, P.W.; et al. Dysregulation of hydrogen sulfide producing enzyme cystathionine γ-lyase contributes to maternal hypertension and placental abnormalities in preeclampsia. *Circulation* **2013**, *127*, 2514–2522. [CrossRef] [PubMed]

54. Holwerda, K.M.; Bos, E.M.; Rajakumar, A.; Ris-Stalpers, C.; vanPampus, M.G.; Timmer, A.; Erwich, J.J.; Faas, M.M.; van Goor, H.; Lely, A.T. Hydrogen sulfide producing enzymes in pregnancy and preeclampsia. *Placenta* **2012**, *33*, 518–521. [CrossRef] [PubMed]

55. Huang, P.L.; Huang, Z.; Mashimo, H.; Bloch, K.D.; Moskowitz, M.A.; Bevan, J.A.; Fishman, M.C. Hypertension in mice lacking the gene for endothelial nitric oxide synthase. *Nature* **1995**, *377*, 239–242. [CrossRef] [PubMed]

56. Yang, G.; Wu, L.; Jiang, B.; Yang, W.; Qi, J.; Cao, K.; Meng, Q.; Mustafa, A.K.; Mu, W.; Zhang, S.; et al. H$_2$S as a physiologic vasorelaxant: Hypertension in mice with deletion of cystathionine gamma-lyase. *Science* **2008**, *322*, 587–590. [CrossRef]

57. Dayal, S.; Bottiglieri, T.; Arning, E.; Maeda, N.; Malinow, M.R.; Sigmund, C.D.; Heistad, D.D.; Faraci, F.M.; Lentz, S.R. Endothelial dysfunction and elevation of S-adenosylhomocysteine in cystathionine beta-synthase-deficient mice. *Circ. Res.* **2001**, *88*, 1203–1209. [CrossRef]

58. Mani, S.; Li, H.; Untereiner, A.; Wu, L.; Yang, G.; Austin, R.C.; Dickhout, J.G.; Lhoták, Š.; Meng, Q.H.; Wang, R. Decreased Endogenous Production of Hydrogen Sulfide Accelerates Atherosclerosis. *Circulation* **2013**, *127*, 2523–2534. [CrossRef]

59. Stout, J.M.; Gousset, M.U.; Drummond, H.A.; Gray, W., 3rd; Pruett, B.E.; Stec, D.E. Sex-specific effects of heme oxygenase-2 deficiency on renovascular hypertension. *J. Am. Soc. Hypertens.* **2013**, *7*, 328–335. [CrossRef]

60. Tain, Y.L.; Hsu, C.N. Targeting on asymmetric dimethylarginine-related nitric oxide-reactive oxygen species imbalance to reprogram the development of hypertension. *Int. J. Mol. Sci.* **2016**, *17*, 2020. [CrossRef]

61. Durante, W. Targeting heme oxygenase-1 in vascular disease. *Curr. Drug Targets* **2010**, *11*, 1504–1516. [CrossRef]

62. Jin, S.; Teng, X.; Xiao, L.; Xue, H.; Guo, Q.; Duan, X.; Chen, Y.; Wu, Y. Hydrogen sulfide ameliorated L-NAME-induced hypertensive heart disease by the Akt/eNOS/NO pathway. *Exp. Biol. Med. (Maywood).* **2017**, *242*, 1831–1841. [CrossRef]

63. Huang, P.; Chen, S.; Wang, Y.; Liu, J.; Yao, Q.; Huang, Y.; Li, H.; Zhu, M.; Wang, S.; Li, L.; et al. Down-regulated CBS/H2S pathway is involved in high-salt-induced hypertension in Dahl rats. *Nitric Oxide* **2015**, *46*, 192–203. [CrossRef]

64. Xiao, L.; Dong, J.-H.; Jing-Hui, D.; Xue, H.-M.; Guo, Q.; Teng, X.; Wu, Y.-M. Hydrogen sulfide improves endothelial dysfunction via downregulating BMP4/COX-2 pathway in rats with hypertension. *Oxid. Med. Cell. Longev.* **2016**, *2016*, 1–10. [CrossRef]

65. Van Goor, H.; Born, J.C.V.D.; Hillebrands, J.-L.; Joles, J.A. Hydrogen sulfide in hypertension. *Curr. Opin. Nephrol. Hypertens.* **2016**, *25*, 107–113. [CrossRef]

66. Paulo, M.; Costa, D.E.F.R.; Bonaventura, D.; Lunardi, C.N.; Bendhack, L.M. Nitric oxide donors as potential drugs for the treatment of vascular diseases due to endothelium dysfunction. *Curr. Pharm. Des.* **2020**, *26*, 3748–3759. [CrossRef] [PubMed]

67. Ndisang, J.F.; Tabien, H.E.; Wang, R. Carbon monoxide and hypertension. *J. Hypertens.* **2004**, *22*, 1057–1074. [CrossRef] [PubMed]

68. Wen, Y.-D.; Wang, H.; Zhu, Y.Z. The Drug developments of hydrogen sulfide on cardiovascular disease. *Oxid. Med. Cell. Longev.* **2018**, *2018*, 4010395. [CrossRef] [PubMed]

69. Beck, K.F.; Pfeilschifter, J. Gasotransmitter synthesis and signalling in the renal glomerulus. Implications for glomerular diseases. *Cell. Signal.* **2021**, *77*, 109823. [CrossRef] [PubMed]

70. Kone, B.C. Nitric oxide synthesis in the kidney: Isoforms, biosynthesis, and functions in health. *Semin. Nephrol.* **2004**, *24*, 299–315. [CrossRef]

71. Wilcox, C.S. Oxidative stress and nitric oxide deficiency in the kidney: A critical link to hypertension? *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2005**, *289*, R913–R935. [CrossRef] [PubMed]

72. Lever, J.M.; Boddu, R.; George, J.F.; Agarwal, A. Heme Oxygenase-1 in Kidney Health and Disease. *Antioxid. Redox Signal.* **2016**, *25*, 165–183. [CrossRef] [PubMed]

73. Ndisang, J.F.; Jadhav, A. Hemin therapy improves kidney function in male streptozotocin-induced diabetic rats: Role of the heme oxygenase/atrial natriuretic peptide/adiponectin axis. *Endocrinology* **2014**, *155*, 215–229. [CrossRef] [PubMed]

74. Mackern-Oberti, J.P.; Llanos, C.; Carreno, L.J.; Riquelme, S.A.; Jacobelli, S.H.; Anegon, I.; Kalergis, A.M. Carbon monoxide exposure improves immune function in lupus-prone mice. *Immunology* **2013**, *140*, 123–132. [CrossRef] [PubMed]

75. Mosley, K.; Wembridge, D.E.; Cattell, V.; Cook, H.T. Heme oxygenase is induced in nephrotoxic nephritis and hemin, a stimulator of heme oxygenase synthesis, ameliorates disease. *Kidney Int.* **1998**, *53*, 672–678. [CrossRef] [PubMed]

76. Ferenbach, D.A.; Ramdas, V.; Spencer, N.; Marson, L.; Anegon, I.; Hughes, J.; Kluth, D.C. Macrophages expressing heme oxygenase-1 improve renal function in ischemia/reperfusion injury. *Mol. Ther.* **2010**, *18*, 1706–1713. [CrossRef] [PubMed]

77. Kie, J.H.; Kapturczak, M.H.; Traylor, A.; Agarwal, A.; Hill-Kapturczak, N. Heme oxygenase-1 deficiency promotes epithelial-mesenchymal transition and renal fibrosis. *J. Am. Soc. Nephrol.* **2008**, *19*, 1681–1691. [CrossRef] [PubMed]

78. Zager, R.A.; Johnson, A.C.; Becker, K. Acute unilateral ischemic renal injury induces progressive renal inflammation, lipid accumulation, histone modification, and "end-stage" kidney disease. *Am. J. Physiol. Renal Physiol.* **2011**, *301*, F1334–F1345. [CrossRef] [PubMed]

79. Dugbartey, G.J. The smell of renal protection against chronic kidney disease: Hydrogen sulfide offers a potential stinky remedy. *Pharm. Rep.* **2018**, *70*, 196–205. [CrossRef] [PubMed]

80. Chen, Y.; Jin, S.; Teng, X.; Hu, Z.; Zhang, Z.; Qiu, X.; Tian, D.; Wu, Y. Hydrogen sulfide attenuates LPS-induced acute kidney injury by inhibiting inflammation and oxidative stress. *Oxid. Med. Cell. Longev.* **2018**, *2018*, 6717212. [CrossRef]

81. Cao, X.; Zhang, W.; Moore, P.K.; Bian, J. Protective smell of hydrogen sulfide and polysulfide in cisplatin-induced nephrotoxicity. *Int. J. Mol. Sci.* **2019**, *20*, 313. [CrossRef]

82. Lin, S.; Visram, F.; Liu, W.; Haig, A.; Jiang, J.; Mok, A.; Lian, D.; Wood, M.E.; Torregrossa, R.; Whiteman, M.; et al. GYY4137, a slow-releasing hydrogen sulfide donor, ameliorates renal damage associated with chronic obstructive uropathy. *J. Urol.* **2016**, *196*, 1778–1787. [CrossRef]

83. Xue, R.; Hao, D.D.; Sun, J.P.; Li, W.W.; Zhao, M.M.; Li, X.H.; Chen, Y.; Zhu, J.H.; Ding, Y.J.; Liu, J.; et al. Hydrogen sulfide treatment promotes glucose uptake by increasing insulin receptor sensitivity and ameliorates kidney lesions in type 2 diabetes. *Antioxid. Redox Signal.* **2013**, *19*, 5–23. [CrossRef]

84. Cirino, G.; Vellecco, V.; Bucci, M. Nitric oxide and hydrogen sulfide: The gasotransmitter paradigm of the vascular system. *Br. J. Pharmacol.* **2017**, *174*, 4021–4031. [CrossRef] [PubMed]

85. Zhong, G.; Chen, F.; Cheng, Y.; Tang, C.; Du, J. The role of hydrogen sulfide generation in the pathogenesis of hypertension in rats induced by inhibition of nitric oxide synthase. *J. Hypertens.* **2003**, *21*, 1879–1885. [CrossRef] [PubMed]

86. Zhou, H.L.; Zhang, R.; Anand, P.; Stomberski, C.T.; Qian, Z.; Hausladen, A.; Wang, L.; Rhee, E.P.; Parikh, S.M.; Karumanchi, S.A.; et al. Metabolic reprogramming by the S-nitroso-CoA reductase system protects against kidney injury. *Nature* **2019**, *565*, 96–100. [CrossRef]

87. Mustafa, A.K.; Gadalla, M.M.; Sen, N.; Kim, S.; Mu, W.; Gazi, S.K.; Barrow, R.K.; Yang, G.; Wang, R.; Snyder, S.H. $H_2S$ signals through protein S-sulfhydration. *Sci. Signal.* **2009**, *2*, ra72. [CrossRef]

88. Stec, D.E.; Drummond, H.A.; Vera, T. Role of carbon monoxide in blood pressure regulation. *Hypertension* **2008**, *51*, 597–604. [CrossRef] [PubMed]

89. Imai, T.; Morita, T.; Shindo, T.; Nagai, R.; Yazaki, Y.; Kurihara, H.; Suematsu, M.; Katayama, S. Vascular smooth muscle cell-directed overexpression of heme oxygenase-1 elevates blood pressure through attenuation of nitric oxide-induced vasodilation in mice. *Circ. Res.* **2001**, *89*, 55–62. [CrossRef]

90. Thorup, C.; Jones, C.L.; Gross, S.S.; Moore, L.C.; Goligorsky, M.S. Carbon monoxide induces vasodilation and nitric oxide release but suppresses endothelial NOS. *Am. J. Physiol.* **1999**, *277*, F882–F889. [CrossRef]

91. Uddin, M.J.; Kim, E.H.; Hannan, M.A.; Ha, H. Pharmacotherapy against oxidative stress in chronic kidney disease: Promising small molecule natural products targeting $Nrf_2$-HO-1 signaling. *Antioxidants* **2021**, *10*, 258. [CrossRef] [PubMed]

92. Fernando, V.; Zheng, X.; Walia, Y.; Sharma, V.; Letson, J.; Furuta, S. S-Nitrosylation: An emerging paradigm of redox signaling. *Antioxidants* **2019**, *8*, 404. [CrossRef]

93. Iciek, M.; Kowalczyk-Pachel, D.; Bilska-Wilkosz, A.; Kwiecień, I.; Górny, M.; Włodek, L. S-sulfhydration as a cellular redox regulation. *Biosci. Rep.* **2015**, *36*, e00304. [CrossRef]

94. Kett, M.M.; Denton, K.M. Renal programming: Cause for concern? *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2011**, *300*, R791–R803. [CrossRef]

95. Nüsken, E.; Dötsch, J.; Weber, L.T.; Nüsken, K.D. Developmental programming of renal function and re-programming approaches. *Front. Pediatr.* **2018**, *6*, 36. [CrossRef] [PubMed]

96. Tain, Y.L.; Hsieh, C.S.; Lin, I.C.; Chen, C.C.; Sheen, J.M.; Huang, L.T. Effects of maternal L-citrulline supplementation on renal function and blood pressure in offspring exposed to maternal caloric restriction: The impact of nitric oxide pathway. *Nitric Oxide* **2010**, *23*, 34–41. [CrossRef] [PubMed]

97. Tain, Y.L.; Huang, L.T.; Hsu, C.N.; Lee, C.T. Melatonin therapy prevents programmed hypertension and nitric oxide deficiency in offspring exposed to maternal caloric restriction. *Oxid. Med. Cell. Longev.* **2014**, *2014*, 283180. [CrossRef] [PubMed]

98. Tain, Y.L.; Lee, W.C.; Hsu, C.N.; Lee, W.C.; Huang, L.T.; Lee, C.T.; Lin, C.Y. Asymmetric dimethylarginine is associated with developmental programming of adult kidney disease and hypertension in offspring of streptozotocin-treated mothers. *PLoS ONE* **2013**, *8*, e55420. [CrossRef]

99. Tain, Y.L.; Hsu, C.N.; Lee, C.T.; Lin, Y.J.; Tsai, C.C. N-Acetylcysteine prevents programmed hypertension in male rat offspring born to suramin-treated mothers. *Biol. Reprod.* **2016**, *95*, 8. [CrossRef]

100. Tain, Y.L.; Lee, W.C.; Wu, K.L.H.; Leu, S.; Chan, J.Y.H. Targeting arachidonic acid pathway to prevent programmed hypertension in maternal fructose-fed male adult rat offspring. *J. Nutr. Biochem.* **2016**, *38*, 86–92. [CrossRef]

101. Hsu, C.N.; Yang, H.W.; Hou, C.Y.; Chang-Chien, G.P.; Lin, S.; Tain, Y.L. Maternal adenine-induced chronic kidney disease programs hypertension in adult male rat offspring: Implications of nitric oxide and gut microbiome derived metabolites. *Int. J. Mol. Sci.* **2020**, *21*, 7237. [CrossRef]

102. Tain, Y.L.; Sheen, J.M.; Chen, C.C.; Yu, H.R.; Tiao, M.M.; Kuo, H.C.; Huang, L.T. Maternal citrulline supplementation prevents prenatal dexamethasone-induced programmed hypertension. *Free Radic. Res.* **2014**, *48*, 580–586. [CrossRef]

103. Tai, I.H.; Sheen, J.M.; Lin, Y.J.; Yu, H.R.; Tiao, M.M.; Chen, C.C.; Huang, L.T.; Tain, Y.L. Maternal N-acetylcysteine therapy regulates hydrogen sulfide-generating pathway and prevents programmed hypertension in male offspring exposed to prenatal dexamethasone and postnatal high-fat diet. *Nitric Oxide* **2016**, *53*, 6–12. [CrossRef] [PubMed]

104. Hsu, C.N.; Lin, Y.J.; Lu, P.C.; Tain, Y.L. Maternal resveratrol therapy protects male rat offspring against programmed hypertension induced by TCDD and dexamethasone exposures: Is it relevant to aryl hydrocarbon receptor? *Int. J. Mol. Sci.* **2018**, *19*, 2459. [CrossRef] [PubMed]

105. Hsu, C.N.; Lin, Y.J.; Tain, Y.L. Maternal exposure to bisphenol A combined with high-fat diet-induced programmed hypertension in adult male rat offspring: Effects of resveratrol. *Int. J. Mol. Sci.* **2019**, *20*, 4382. [CrossRef] [PubMed]

106. Gwathmey, T.M.; Shaltout, H.A.; Rose, J.C.; Diz, D.I.; Chappell, M.C. Glucocorticoid-induced fetal programming alters the functional complement of angiotensin receptor subtypes within the kidney. *Hypertension* **2011**, *57*, 620–626. [CrossRef] [PubMed]

107. Hsu, C.N.; Hou, C.Y.; Chang-Chien, G.P.; Lin, S.; Tain, Y.L. Maternal garlic oil supplementation prevents high-fat diet-induced hypertension in adult rat offspring: Implications of H$_2$S-generating pathway in the gut and kidneys. *Mol. Nutr. Food Res.* **2021**, *65*, e2001116. [CrossRef] [PubMed]

108. Hsu, C.-N.; Hou, C.-Y.; Chang-Chien, G.-P.; Lin, S.; Tain, Y.-L. Maternal N-Acetylcysteine Therapy Prevents Hypertension in Spontaneously Hypertensive Rat Offspring: Implications of Hydrogen Sulfide-Generating Pathway and Gut Microbiota. *Antioxidants* **2020**, *9*, 856. [CrossRef]

109. Tain, Y.L.; Chan, S.H.H.; Chan, J.Y.H. Biochemical basis for pharmacological intervention as a reprogramming strategy against hypertension and kidney disease of developmental origin. *Biochem. Pharmacol.* **2018**, *153*, 82–90. [CrossRef]

110. Tain, Y.L.; Hsu, C.N. Interplay between oxidative stress and nutrient sensing signaling in the developmental origins of cardiovascular disease. *Int. J. Mol. Sci.* **2017**, *18*, E841. [CrossRef]

111. Hsu, C.N.; Tain, Y.L. Targeting the renin-angiotensin-aldosterone system to prevent hypertension and kidney disease of developmental origins. *Int. J. Mol. Sci.* **2021**, *22*, 2298. [CrossRef]

112. Koeners, M.P.; van Faassen, E.E.; Wesseling, S.; Sain-van der Velden, M.; Koomans, H.A.; Braam, B.; Joles, J.A. Maternal supplementation with citrulline increases renal nitric oxide in young spontaneously hypertensive rats and has long-term antihypertensive effects. *Hypertension* **2007**, *50*, 1077–1084. [CrossRef]

113. Wu, Z.; Siuda, D.; Xia, N.; Reifenberg, G.; Daiber, A.; Münzel, T.; Förstermann, U.; Li, H. Maternal treatment of spontaneously hypertensive rats with pentaerythritoltetranitrate reduces blood pressure in female offspring. *Hypertension* **2015**, *65*, 232–237. [CrossRef]

114. Wesseling, S.; Essers, P.B.; Koeners, M.P.; Pereboom, T.C.; Braam, B.; van Faassen, E.E.; Macinnes, A.W.; Joles, J.A. Perinatal exogenous nitric oxide in fawn-hooded hypertensive rats reduces renal ribosomal biogenesis in early life. *Front. Genet.* **2011**, *2*, 52. [CrossRef] [PubMed]

115. Tain, Y.L.; Leu, S.; Lee, W.C.; Wu, K.L.H.; Chan, J.Y.H. Maternal melatonin therapy attenuated maternal high-fructose combined with post-weaning high-salt diets-induced hypertension in adult male rat offspring. *Molecules* **2018**, *23*, E886. [CrossRef] [PubMed]

116. Hsu, C.N.; Lee, C.T.; Huang, L.T.; Tain, Y.L. Aliskiren in early postnatal life prevents hypertension and reduces asymmetric dimethylarginine in offspring exposed to maternal caloric restriction. *J. Renin Angiotensin Aldosterone Syst.* **2015**, *16*, 506–513. [CrossRef] [PubMed]

117. Uson-Lopez, R.A.; Kataoka, S.; Mukai, Y.; Sato, S.; Kurasaki, M. Melinjo (Gnetum gnemon) Seed extract consumption during lactation improved vasodilation and attenuated the development of hypertension in female offspring of fructose-fed pregnant rats. *Birth Defects Res.* **2018**, *110*, 27–34. [CrossRef]

118. Hsu, C.N.; Lin, Y.J.; Yu, H.R.; Lin, I.C.; Sheen, J.M.; Huang, L.T.; Tain, Y.L. Protection of male rat offspring against hypertension programmed by prenatal dexamethasone administration and postnatal high-fat diet with the Nrf$_2$ activator dimethyl fumarate during pregnancy. *Int. J. Mol. Sci.* **2019**, *20*, 3957. [CrossRef]

119. Guo, Q.; Feng, X.; Xue, H.; Jin, S.; Teng, X.; Duan, X.; Xiao, L.; Wu, Y. Parental renovascular hypertension-induced autonomic dysfunction in male offspring is improved by prenatal or postnatal treatment with hydrogen sulfide. *Front. Physiol.* **2019**, *10*, 1184. [CrossRef]

120. Xiao, D.; Huang, X.; Li, Y.; Dasgupta, C.; Wang, L.; Zhang, L. Antenatal antioxidant prevents nicotine-mediated hypertensive response in rat adult offspring. *Biol. Reprod.* **2015**, *93*, 66. [CrossRef]

121. Xiao, D.; Wang, L.; Huang, X.; Li, Y.; Dasgupta, C.; Zhang, L. Protective effect of antenatal antioxidant on nicotine-induced heart ischemia-sensitive phenotype in rat offspring. *PLoS ONE* **2016**, *11*, e0150557. [CrossRef]

122. Sengupta, P. The laboratory rat: Relating its age with human's. *Int. J. Prev. Med.* **2013**, *4*, 624–630.

123. Luiking, Y.C.; Ten Have, G.A.M.; Wolfe, R.R.; Deutz, N.E.P. Arginine de novo and nitric oxide production in disease states. *Am. J. Physiol. Endocrinol. Metab.* **2012**, *303*, E1177–E1189. [CrossRef] [PubMed]

124. Rodrigues-Krause, J.; Krause, M.; Rocha, I.M.G.D.; Umpierre, D.; Fayh, A.P.T. Association of l-arginine supplementation with markers of endothelial function in patients with cardiovascular or metabolic disorders: A systematic review and meta-analysis. *Nutrients* **2018**, *11*, 15. [CrossRef] [PubMed]

125. Racasan, S.; Braam, B.; van der Giezen, D.M.; Goldschmeding, R.; Boer, P.; Koomans, H.A.; Joles, J.A. Perinatal L-arginine and antioxidant supplements reduce adult blood pressure in spontaneously hypertensive rats. *Hypertension* **2004**, *44*, 83–88. [CrossRef]

126. Koeners, M.P.; Braam, B.; van der Giezen, D.M.; Goldschmeding, R.; Joles, J.A. Perinatal micronutrient supplements ameliorate hypertension and proteinuria in adult fawn-hooded hypertensive rats. *Am. J. Hypertens.* **2010**, *23*, 802–808. [CrossRef]

127. Cynober, L.; Moinard, C.; De Bandt, J.P. The 2009 ESPEN Sir David Cuthbertson. Citrulline: A new major signaling molecule or just another player in the pharmaconutrition game? *Clin. Nutr.* **2010**, *29*, 545–551. [CrossRef]

128. Hopper, C.P.; Zambrana, P.N.; Goebel, U.; Wollborn, J. A brief history of carbon monoxide and its therapeutic origins. *Nitric Oxide* **2021**, *111–112*, 45–63. [CrossRef] [PubMed]

129. Funes, S.C.; Rios, M.; Fernández-Fierro, A.; Covián, C.; Bueno, S.M.; Riedel, C.A.; Mackern-Oberti, J.P.; Kalergis, A.M. Naturally derived heme-oxygenase 1 inducers and their therapeutic application to immune-mediated diseases. *Front. Immunol.* **2020**, *11*, 1467. [CrossRef] [PubMed]

130. Robledinos-Antón, N.; Fernández-Ginés, R.; Manda, G.; Cuadrado, A. Activators and inhibitors of NRF$_2$: A review of their potential for clinical development. *Oxid. Med. Cell. Longev.* **2019**, *2019*, 9372182. [CrossRef]

131. Liao, J.X.; Chen, Y.W.; Shih, M.K.; Tain, Y.L.; Yeh, Y.T.; Chiu, M.H.; Chang, S.K.C.; Hou, C.Y. Resveratrol butyrate esters inhibit bpa-induced liver damage in male offspring rats by modulating antioxidant capacity and gut microbiota. *Int. J. Mol. Sci.* **2021**, *22*, 5273. [CrossRef]

132. Tain, Y.-L.; Hsu, C.-N.; Lu, P.-C. Early short-term treatment with exogenous hydrogen sulfide postpones the transition from prehypertension to hypertension in spontaneously hypertensive rat. *Clin. Exp. Hypertens.* **2017**, *40*, 58–64. [CrossRef]

133. Hsu, C.N.; Lin, Y.J.; Lu, P.C.; Tain, Y.L. Early supplementation of D-cysteine or L-cysteine prevents hypertension and kidney damage in spontaneously hypertensive rats exposed to high-salt intake. *Mol. Nutr. Food Res.* **2018**, *62*, 2. [CrossRef] [PubMed]

134. Zhu, Y.; Anand, R.; Geng, X.; Ding, Y. A mini review: Garlic extract and vascular diseases. *Neurol. Res.* **2018**, *40*, 421–425. [CrossRef] [PubMed]

135. Bełtowski, J. Hydrogen sulfide in pharmacology and medicine—An update. *Pharmacol. Rep.* **2015**, *67*, 647–658. [CrossRef] [PubMed]