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17-Hydroxyprogesterone caproate improves hypertension and renal endothelin-1 in response to sFlt-1 induced hypertension in pregnant rats

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Abstract

Preeclampsia (PE) is characterized by new onset hypertension in association with elevated soluble fms-like tyrosine kinase-1 (sFlt-1) and preproendothelin-1 (PPET-1) levels. Currently there is no effective treatment for PE except for early delivery of the fetal placental unit, making PE a leading cause for premature births worldwide. Administration of 17-hydroxyprogesterone caproate (17-OHPC) is used for prevention of recurrent preterm birth. This study was designed to test the hypothesis that 17-OHPC improves hypertension and ET-1 in response to elevated sFlt-1 in pregnant rats. sFlt-1 was infused into normal pregnant (NP) Sprague-Dawley rats (3.7 $\mu g \cdot kg^{-1} \cdot day^{-1}$ for 6 days, gestation days 13–19) in the presence or absence of 17-OHPC (3.32 mg/kg) administered via intraperitoneal injection on gestational days 15 and 18. Mean arterial blood pressure (MAP), pup and placenta weights, renal cortex PPET-1 mRNA levels and nitrate-nitrite levels were measured on GD 19. Infusion of sFlt-1 into NP rats elevated mean arterial pressure (MAP) compared with control NP rats: 115 ± 1 (n = 13) vs. 99 ± 2 mmHg (n = 12, $p < 0.05$). 17-OHPC attenuated this hypertension reducing MAP to 102 ± 3 mmHg in sFlt-1 treated pregnant rats (n = 8). Neither pup nor placental weight was affected by sFlt-1 or 17-OHPC. Importantly, renal cortex PPET-1 mRNA levels were elevated 3 fold in NP + sFlt-1 rats compare to NP rats, which decreased with 17-OHPC administration. Plasma nitrate-nitrite levels were 44 ± 9 μM in NP rats (n = 9), 20 ± 3 μM in NP + sFlt-1 (n = 7), which increased to 42 ± 11 μM NP + sFlt-1 + 17OHPC (n = 6). Administration of 17-OHPC improves clinical characteristics of preeclampsia in response to elevated sFlt-1 during pregnancy.

Keywords

Preproendothelin-1; sFlt-1; 17-OHPC; Preeclampsia

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

1. Introduction

Preeclampsia (PE) is a multi-system hypertensive disorder characterized by fetal growth restriction, preterm birth, placental abruption, HELLP syndrome, eclampsia, cardiovascular disease, and end-organ damage [1]. PE complicates approximately 10% of all pregnancies, is a significant contributor to maternal and perinatal morbidity, and remains a leading cause of iatrogenic preterm birth [1,2]. Delivery of the fetal-maternal unit remains the only definitive cure of PE despite many years of research, and further treatment strategies are needed [3]. Interventions that could safely and effectively prolong pregnancy and reduce the risk of iatrogenic preterm birth has the potential to significantly improve maternal and fetal antenatal care.

The diagnosis of PE is made by new onset hypertension with additional evidence of multi-system vascular dysfunction [4]. This vascular dysfunction manifests clinically as hypertension, proteinuria, worsening kidney function, neurological symptoms, hemolysis, blood clotting disorders, and increased vascular resistance. On a cellular and molecular level, the disorder is marked by deficiency of trophoblast invasion and placental ischemia, ultimately resulting in decreased vasodilators, increased inflammatory cytokines, chronic immune activation, and imbalance in circulating angiogenic factors [3,5–13].

In PE the imbalance and dysregulation between proangiogenic and antiangiogenic factors is thought to be a main contributing factor to the laboratory signs and clinical manifestations associated with the disorder [14]. Placental growth factor (PIGF) and soluble fms-like tyrosine-1 (sFlt-1) are two important biomarkers of placental function and PE [13]. sFlt-1 is an antiangiogenic factor notoriously associated with intrauterine growth restriction (IUGR) and PE [15]. *In vivo* studies have shown that women with PE have lower concentrations of PIGF and higher concentrations of sFlt-1 compared to control subjects [13,16–18]. Utilizing a ratio between antiangiogenic sFlt-1 and proangiogenic placental growth factor (PIGF), there are ongoing investigations into utilization of these placental biomarkers to predict PE [19–22]. Disordered angiogenesis is a hallmark of PE and restoration of the balance between proangiogenic and antiangiogenic factors is hypothesized to be a possible treatment option.

Endothelin-1, also known as preproendothelin-1, is produced and secreted by endothelial cells [23]. It is a potent vasoconstrictor and acts in concert with the vasodilator nitric-oxide to maintain vascular tone [23]. Endothelin-1 is known to contribute to the pathophysiology of PE with studies demonstrating that ET-1 is increased in PE [24]. Attenuation of the endothelin axis and blockage of endothelin-1 is now being considered a treatment option for PE [25]. The effect of progesterone supplementation on modulating the relationship between endothelin-1 as a vasoconstrictor and nitric-oxide as a vasodilator is an area of great interest in furthering our understanding of PE.

Progesterone supplementation through a progesterone derivative, such as 17-OHPC, has been used for many years to lower the recurrence risk of preterm birth [26–29]. The utilization of 17-OHPC in patients at risk of PE or for those who have already developed the clinical manifestations of preterm PE is still an area needing further exploration, and the benefit of 17-OHPC to reduce placental ischemia has not yet been clearly

defined [26,30]. Previous data from Kiprono et al indicate that women with PE have lower levels of progesterone when compared to gestational age- and race-matched non-PE control pregnant women [31,32]. Furthermore, studies have shown that supplementation of RUPP rat model of PE with 17-OHPC decreases blood pressure and inflammation, with attenuation of pro-inflammatory cytokines that accompany an increase of NO bioavailability [33,34]. Improvement in UARI, litter size, IUGR and hypertension in response to placental ischemia was also demonstrated. More recent studies by Amaral et al. have shown that supplementation of 17-OHPC in the RUPP model increased NO bioavailability while decreasing sFlt-1 [35].

This current study was designed to test the hypothesis that 17-OHPC improves hypertension and ET-1 in response to sFlt-1 induced hypertension in pregnant rats.

2. Materials and methods

Pregnant Sprague-Dawley rats purchased from Harlan Sprague Dawley (Indianapolis, IN) were used in this study. Animals were housed in a temperature-controlled room (23 °C) with a 12:12-h light–dark cycle with free access to standard rat chow and water. All experimental procedures executed in this study were in accordance with the National Institutes of Health guidelines for use and care of animals. All protocols were approved by the Institutional Animal Care and Use Committee at the University of Mississippi Medical Center.

2.1. sFlt-1 induced hypertension

Surgical procedures were carried out under appropriate anesthesia, 2% isoflurane, and analgesics were given post-operatively as needed. Pregnant rat dams weighting approximately 200–250 g were randomly assigned to either Normal pregnant + sFlt-1 or NP control groups. sFlt-1 (recombinant mouse VEGF R1/Flt-1 Fc Chimera, R&D Systems catalog # 471-F1–100) miniosmotic pump was infused into normal pregnant (NP) Sprague-Dawley rats (3.7 $\mu g \cdot kg^{-1} \cdot day^{-1}$ for 6 days, gestation days 13–19) as described previously [36] in the presence or absence of 17-OHPC. Also analgesics were used to provide comfort for the surgical rats include 0.25% sensor care administered topically or 5 mg/kg Carprofen administered via subcutaneous injection, once daily for 2–3 days following surgical procedure.

2.2. Administration of 17-OHPC

A subset of sFlt-1 pregnant rats were injected with 17-hydroxyprogesterone caproate (17-OHPC) at days 15 (first injection) and 18 of gestation (second injection). The 17-OHPC (Makena, AMAG Pharmaceuticals) was administered intraperitoneal as 0.5 cm^3 solution of 3.32 mg/kg 17-OHPC to pregnant rats as described previously [32]. This dose is equivalent to a typical human dose for the prevention of preterm labor and has been demonstrated to be effective in rat models of PE [32,34,35]. We have shown that 17-OHPC had no blood pressure effects on NP rats and therefore 17-OHPC was not administered to NP rats in this study [35].

2.3. Measurement of mean arterial blood pressure

On day 18 of gestation, using the isoflurane anesthesia (Webster, Sterling, MA), carotid arterial catheters were inserted for blood pressure measurements. The catheters inserted were V3 tubing (SCI, Scientific Commodities, Inc., Lake Havasu City, AZ), which is tunneled to the back of the neck and exteriorized. On day 19 of gestation, mean arterial blood pressure was analyzed after placing the rats in individual restraining cages. Arterial pressure was monitored with a pressure transducer (Cobe III tranducer CDX Sema) and recorded continuously for 30 min after a 30-min stabilization period. Subsequently, blood samples were collected, tissues were harvested, and placenta and pup weights were recorded under anesthesia.

2.4. Determination of circulating nitrate–nitrite levels

Plasma collected from all pregnant rats was utilized to measure nitrate-nitrite levels using Nitrate/Nitrite Colorimetric Assay Kit from Cayman Chemical following instructions outlined by the manufacturer. The inter-assay coefficient of variation is 3.4% while intra-assay coefficient of variation is 2.7%.

2.5. Determination of renal cortex preproendothelin-1 mRNA levels

Real-time polymerase chain reaction (qRT-PCR) was used to determine renal cortex preproendothelin-1 (PPET-1) levels. The tissues were stored at −80 °C. Total RNA was then extracted from the homogenized tissues using the RNeasy Protect Mini Kit (Qiagen). The isolation procedure was performed according to the manufacturer's provided instructions. After RNA was isolated, concentration and quality were verified using a spectrophotometer (Eppendorf BioPhotometer). cDNA was synthesized from 1 μg of RNA using the iScript cDNA Synthesis Kit (BioRad). Real-time polymerase chain reaction (qRT-PCR) was performed using iQ SYBR Green Supermix (BioRad) and the CFX96 Touch Real-Time PCR Detection System (BioRad). The following primer sequences provided by Life technologies were used for PPET: forward 1, CTAGGTCTAAGCGATCCTTG, and reverse 1, TCTTTGTCTGCTTGGC. Levels of mRNA were calculated using the mathematical formula $2^{-\Delta\Delta Ct}$ ($2^{\text{avg. Ct gene of interest} - \text{avg Ct beta actin}}$) recommended by Applied Biosystems (Applied Biosystems User Bulletin, No. 2, 1997).

2.6. Statistical analysis

All of the data are expressed as mean ± SEM. Comparisons of control with experimental groups were analyzed by one-way ANOVA with Bonferroni multiple comparisons test as post hoc analysis. A value of $p < 0.05$ was considered statistically significant.

3. Results

Infusion of sFlt-1 into NP rats elevated mean arterial pressure (MAP) compared with control NP rats: 117 ± 1 (n = 13) vs. 99 ± 2 mmHg (n = 12, $p < 0.05$). Administration of 17-OHPC blunted the hypertension lowering MAP to 102 ± 3 mmHg in sFlt-1 treated pregnant rats (n = 8, Fig. 1). 17-OHPC did not change pup, placenta weights or litter size in response to sFlt-1 during pregnancy (Fig. 2).

Importantly, renal cortex PPET-1 mRNA levels were elevated 3 fold in NP + sFlt-1 rats compare to NP rats, which was normalized with 17-OHPC administration, (n = 5–7/group, $p < 0.05$, Fig. 3).

Plasma nitrate-nitrite levels were 44 ± 9 μM in NP rats (n = 9), 20 ± 3 μM in NP + sFlt-1 (n = 7), which increased to 42 ± 11 μM NP + sFlt-1 + 17OHPC (n = 6). Neither pup nor placental weight was affected by sFlt-1 or 17-OHPC. We have recently published that 17-OHPC given to NP rats did not show any difference in pregnancy outcomes when compared with untreated NP rats [35] (Fig. 4).

4. Discussion

The principal findings of this study are: 17-OHPC administered at days 15 and 18 of gestation into sFlt-1 induced hypertension in pregnant rats reduces blood pressure and renal ET-1 while elevating circulating nitrate-nitrite levels.

Progesterone is an endogenous steroid and sex hormone that plays a critical role in the maintenance of normal pregnancy. In addition to its many other function, progesterone has anti-inflammatory as well as vasodilatory effects [31,37,38]. The ability of progesterone to modulate the immune system is two-fold, determined by the availability of the hormone or progesterone sensitivity of the lymphocytes [39]. It is believed the mechanism of action of 17-OHPC involves interaction with the progesterone receptors, facilitating an increase in nitric oxide production and resultant promotion of uterine relaxation.

Prior data showed that 17-OHPC administration on day 18 of gestation in the RUPP rat model improved hypertension in RUPP rats which was associated with improved inflammation by attenuating $CD4^+$ T cells and other pro-inflammatory cytokines. Improvements were also noted in renal and placental ET-1, UARI, litter size, vascular eNOS expression and nitric oxide (NO) bioavailability [32–34].

Pregnancy is associated with immuno-modulation in order to assure a successful and healthy pregnancy. Preeclampsia is associated with physiologic alterations resulting in a state of chronic inflammation [6,8,11,40]. This state of chronic inflammation plays an important role in the pathophysiology of PE, with increased inflammatory mediators, and imbalance in circulating angiogenic factors. These factors have been shown to play an important role in stimulating vasoactive pathways such as endothelin-1 (ET-1), AT1-AA and sFlt-1 and oxidative stress, while reducing vasodilatory factors such as nitric oxide [9,31,41–43].

The exact mechanism by which sFlt-1 production leads to hypertension is an area of current investigation [14,36]. It has been demonstrated that sFlt-1 increases in response to placental ischemia via AT1 receptor activation by endogenous ANGII [44]. Furthermore, our lab has shown that infusion of agonistic autoantibodies to the angiotensin II type I receptor (AT1-AA) significantly increased endothelin-1 in renal cortices and placenta, as well as increasing sFlt-1 compared to normal pregnant controls [45].

Studies have been performed attempting to restore the balance between the antiangiogenic sFlt-1 and angiogenic placental growth factor (PIGF) [46]. Zhu et al infused PIGF into

the RUPP rat model and demonstrated that restoring the angiogenic/antiangiogenic balance by infusing PIGF decreased vasoconstriction while improving blood pressure [46]. The mechanism by which PIGF infusion decreases blood pressure is through enhancement of endothelial nitric oxide cGMP pathway [46].

The endothelin type A receptor has been hypothesized as a potential target for therapeutics in treating PE [24]. Murphy et al explored the relationship between sFlt-1 and ET-1 by infusion of sFlt-1 into pregnant rats and pregnant rats treated with a selective endothelin type 1 receptor antagonist [36]. In their study, sFlt-1 infusion into pregnant rats causes hypertension and increases ET-1 mRNA expression in the renal cortices by approximately 3-fold compared to normal pregnant rats. Endothelin type A receptor blockade completely mitigated blood pressure response in sFlt-1 infused rats, and had no effect on blood pressure in normal pregnant rats [36]. In agreement with it, an important finding of this current study is that 17-OHPC improves pregnancy outcomes in response to sFlt-1 induced hypertension in pregnant rats.

5. Conclusion

This study demonstrated that 17-OHPC improves hypertension in response to elevated sFlt-1 in pregnant rats. Furthermore, 17-OHPC improved renal cortex PPET-1 and NO levels. More studies are needed to investigate the role of progesterone in regards to modulation of sFlt-1 induced hypertension and attenuation of renal preproendothelin-1 in PE.

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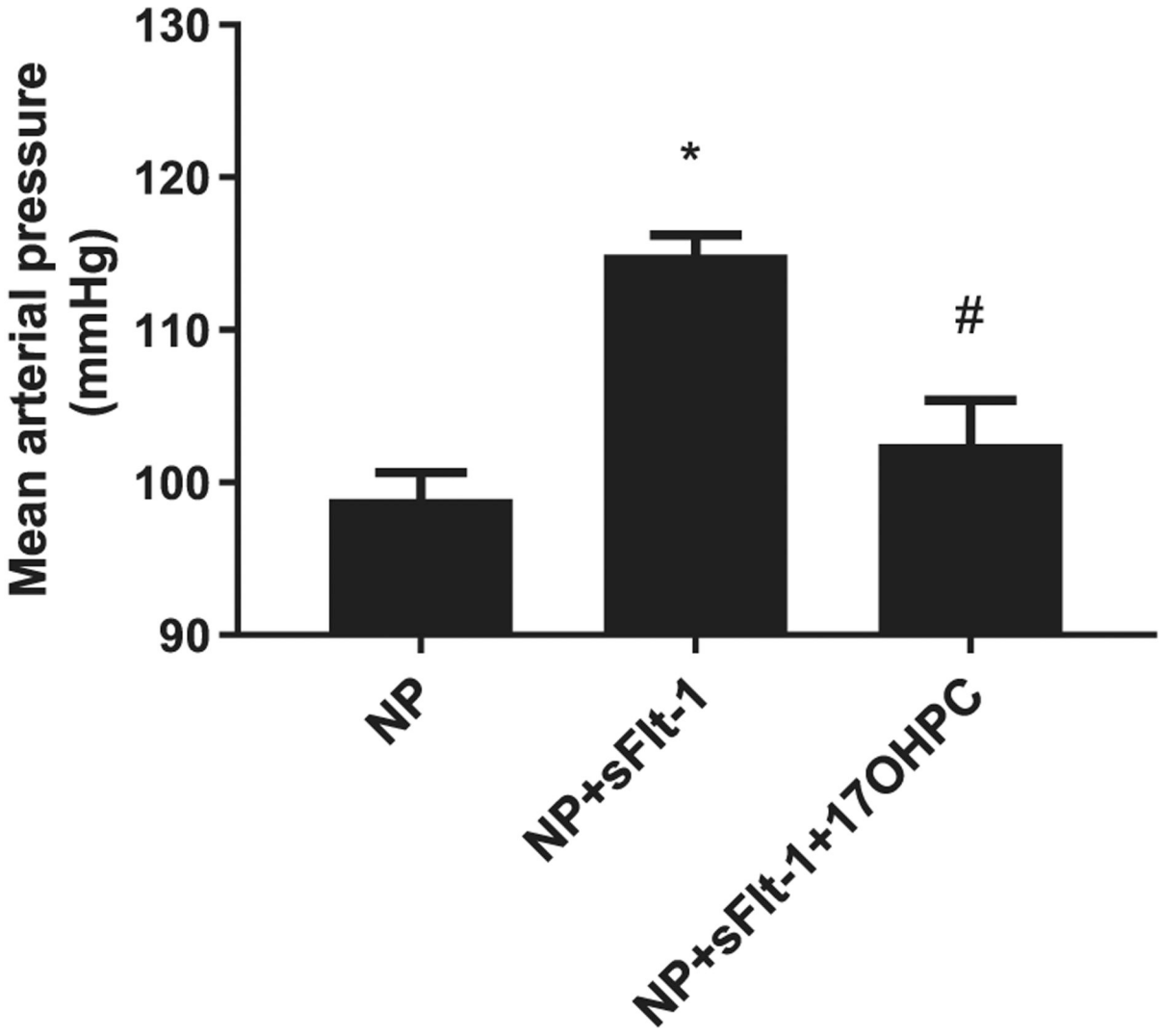

Fig. 1.

17-OHPC reduces mean arterial blood pressure (MAP) in response to sFlt-1 induced hypertension in pregnant rats (n = 11–17/group). Data are shown as means ± S.E.M. *p < 0.05 vs. NP, $^{\#}p < 0.05$ vs. NP + sFlt-1. One-way ANOVA and Bonferroni as post hoc analysis were performed to generate *p* values.

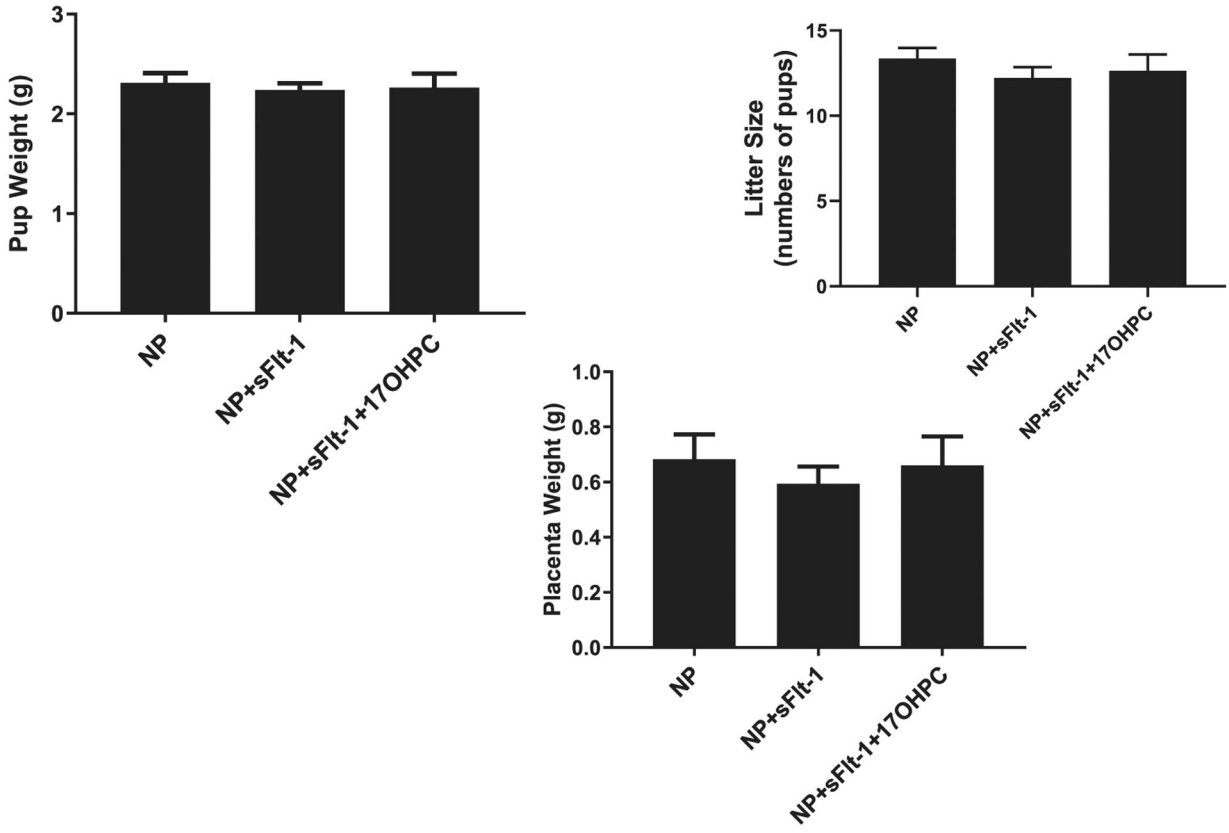

Fig. 2.

17-OHPC did not change either pup (panel A) or placenta weights (panel B) in response to sFlt-1 induced hypertension in pregnant rats (n = 11–17/group). Data are shown as means ± S.E.M. One-way ANOVA and Bonferroni as post hoc analysis were performed to generate *p* values.

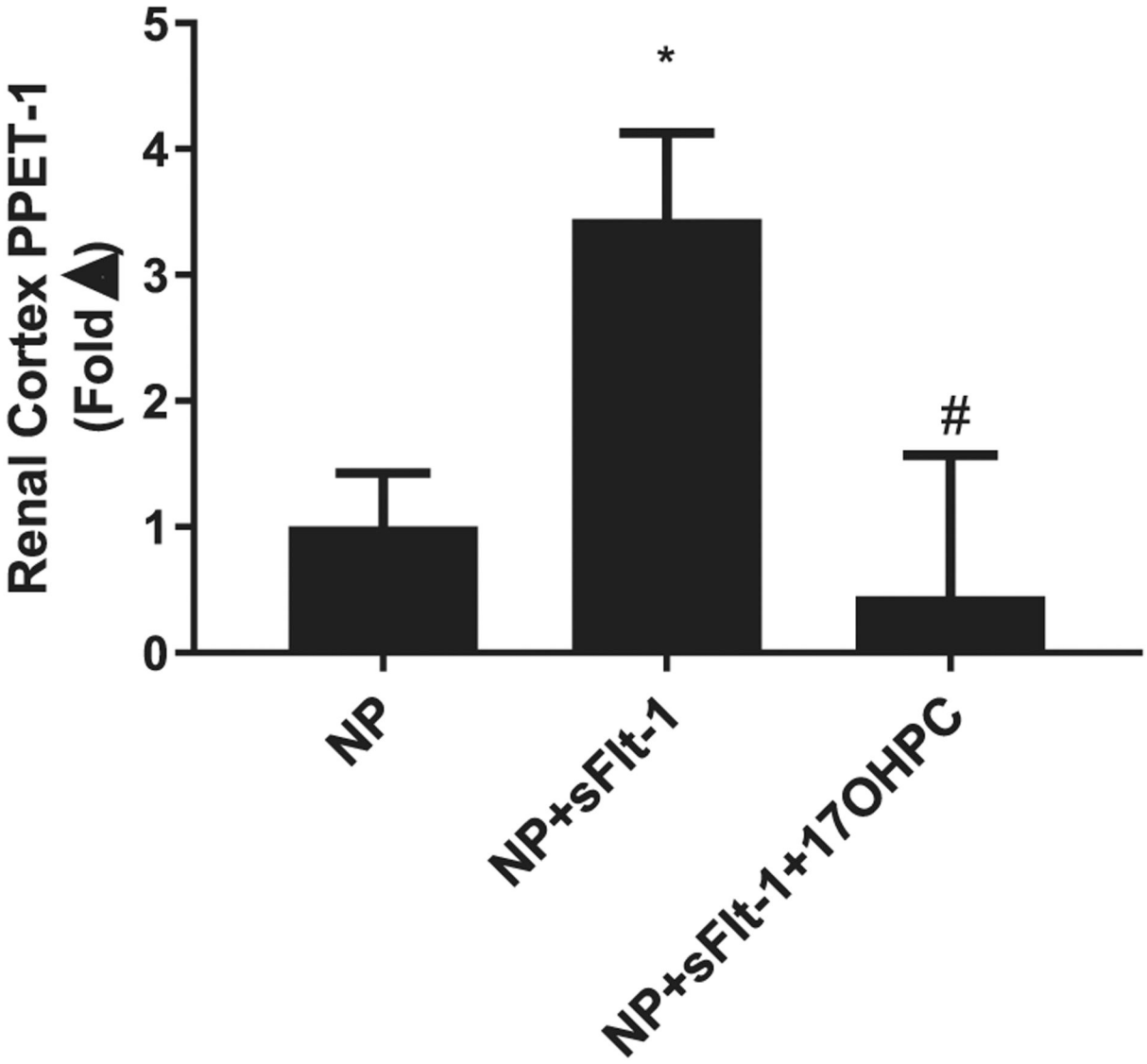

Fig. 3.

17-OHPC improves renal cortex PPET-1 (n = 5–7/group). Data are shown as means ± S.E.M. *p < 0.05 vs. NP, #p < 0.05 vs. NP + sFlt-1. One-way ANOVA and Bonferroni as post hoc analysis were performed to generate *p* values.

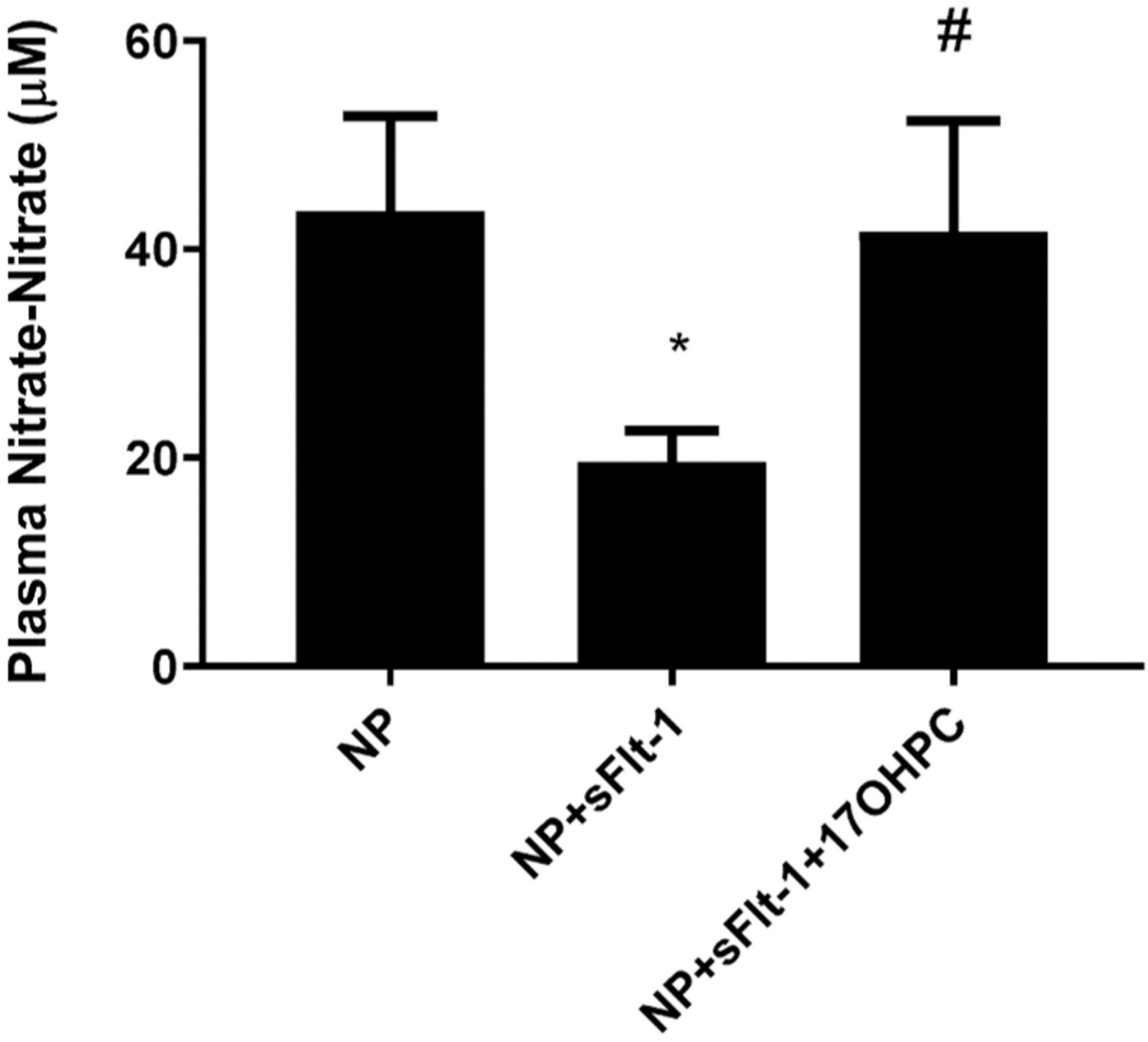

Fig. 4.

17-OHPC increases circulating nitrate-nitrite levels (n = −6–9/group) in response to sFlt-1 during pregnancy. Data are shown as means ± S.E.M. One-way ANOVA and Bonferroni as post hoc analysis were performed to generate *p* values.