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Original Research Article

Influence of the selective COX-2 inhibitor celecoxib on sex differences in blood pressure and albuminuria in spontaneously hypertensive rats

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ABSTRACT

We previously reported that female spontaneously hypertensive rats (SHR) have greater cyclooxygenase-2 (COX-2) expression in the renal medulla and enhanced urinary excretion of prostaglandin (PG) E_2 (PGE_2) metabolites compared to male SHR. Based on the role of COX-2-derived prostanoids in the regulation of cardiovascular health, the aim of the current study was to test the hypothesis that blood pressure (BP) in female SHR is more sensitive to COX-2 inhibition than in males. Seven week old male and female SHR were implanted with telemetry transmitters for continuous BP recording. After one week of baseline BP recording, male and female SHR were randomized to receive the selective COX-2 inhibitor celecoxib (10 mg/kg/day) or vehicle for six weeks (from 9 to 14 weeks of age). Female SHR had lower BP and albuminuria compared to male SHR as well as enhanced urinary excretion of PGE metabolite (PGEM), 6-keto $PGF_{1\alpha}$ and thromboxane B_2, indicators of PGE_2, PGI_2 and TXA_2, respectively. Treatment with celecoxib did not significantly alter BP or albuminuria in either female or male SHR. Celecoxib did not change PGs metabolites excretion in male SHR; however, excretion levels of PGEM and 6-keto $PGF_{1\alpha}$ were reduced in female SHR. COX-2 derived PG can also induce oxidative stress. Markers of oxidative stress (thiobarbituric acid reactive substances (TBARs) and H_2O_2 excretion) were lesser in female SHR versus male SHR. Celecoxib treatment did not significantly change markers of oxidative stress in female SHR, however, urinary TBARs excretion was significantly reduced in male SHR after 6 weeks of treatment with celecoxib. Therefore, although celecoxib treatment appears to have distinct effects on prostanoids levels in female SHR vs. males, it is unlikely that COX-2 contributes to established sex differences in BP in SHR.

1. Introduction

Spontaneously hypertensive rats (SHR) are among the most commonly used experimental animal model to study sex differences in hypertension. SHR recapitulate the gender difference observed in blood pressure (BP) clinically where men have higher BP than women through much of life regardless of race and ethnicity [1–3]. Although different pathways have been linked to observed sex differences in BP, the exact mechanisms responsible have yet to be fully defined.

Cyclooxygenase (COX)-derived prostaglandins (PGs) play an important role in the regulation of cardiovascular and renal health [4] by contributing to the maintenance of renal function, fluid homeostasis, and BP control [5]. COX enzymes mediate the production of PGs from arachidonic acid and there are two COX isoforms, COX-1 and COX-2. COX-1 and COX-2 have similar biological activity but distinct cellular expression and regulation [6]. COX-1 is constitutively expressed while COX-2 expression is induced by inflammation, although there is also evidence to support a role for COX-2 in kidney development, ovulation, parturition, and cardiovascular homeostasis. COX-2 mediates the production of vasoactive eicosanoids including TXA_2 which is potent vasoconstrictor as well as PGE_2 and prostacyclin (PGI_2) which are vasodilators [5]. Within the kidney, PGI_2 and PGE_2 are produced by vascular and tubular structures and serve as mediators of medullary blood flow and renal salt handling [5]. We have previously reported sex differences in COX-2 and PGs production in SHR with no difference in COX-1 expression where female SHR have greater COX-2 expression in the renal medulla and enhanced urinary excretion of PGE_2 metabolites compared with male SHR [7]. There are also well established sex differences in BP and protein excretion in SHR where young adult males have a high BP and greater protein excretion compared to age matched

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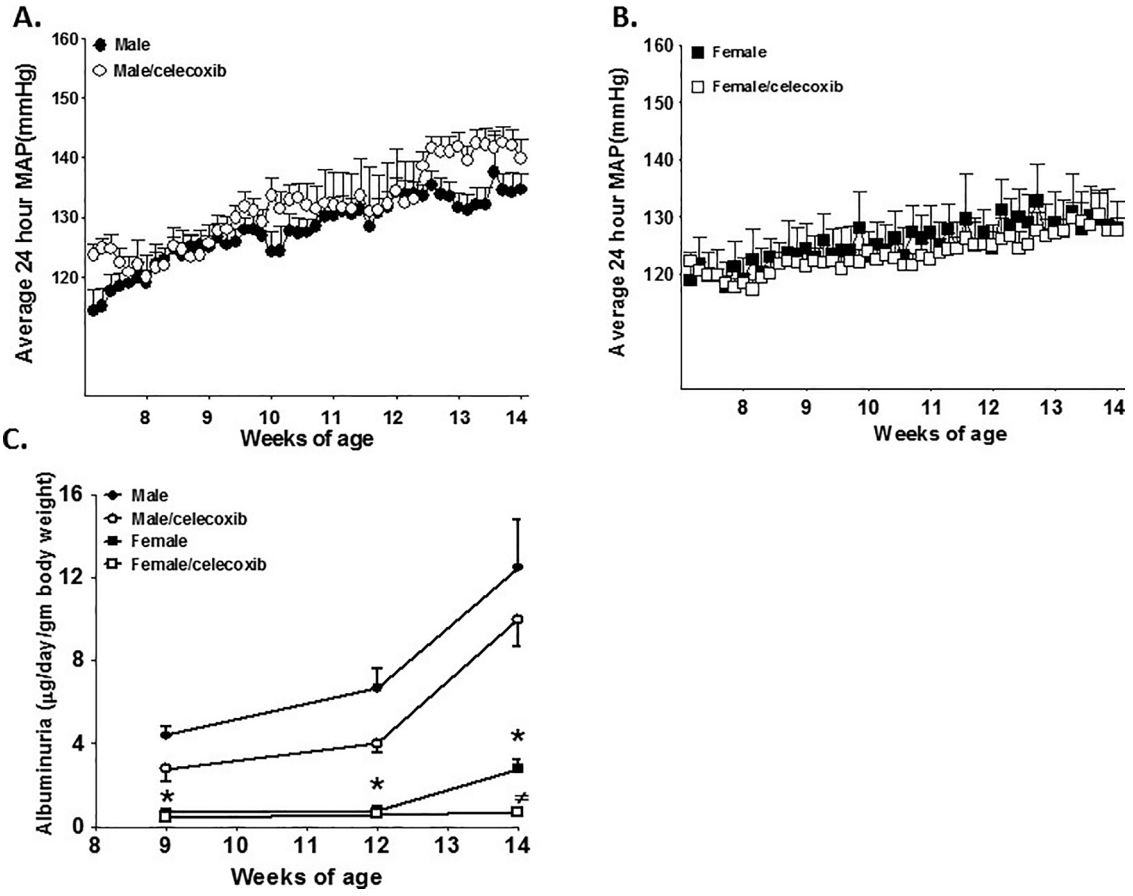

Fig. 1. Effect of celecoxib, the selective COX-2 inhibitor, treatment for 6 weeks on the average 24 h mean arterial pressure (MAP) in male (A) and female SHR (B) as well as on the progression of albuminuria in male and female SHR (C). (n = 5–8 for telemetry and n = 7–8 for albuminuria; $^{*}P < 0.05$ versus corresponding male SHR and $^{\#}P < 0.05$ versus corresponding female SHR).

females [8,9].

Clinically, COX-2 inhibitors have been used to provide analgesic and anti-inflammatory effects [10]; however, COX-2 inhibitors have also been shown to result in hypertension [11,12] thereby further implicating a role for COX-2 in maintaining BP. Based on our previous findings of greater medullary COX-2 expression in female SHR coupled with lower BP when compared to male SHR [7], the goal of the current study was to test the hypothesis that BP in female SHR will be more sensitive to the selective COX-2 inhibitor celecoxib than in males. Moreover, we and others have previously shown a sex difference in oxidative stress in SHR with females having lower renal oxidative stress levels than males [13,14]. Because COX-2 might enhance prostanoids-dependent effect on oxidative stress [15,16], our study will also test whether celecoxib treatment will modulate sex difference in oxidative stress in SHR.

2. Material and methods

Male and female SHR were used in this study (n = 7–8/group; Harlan). All experiments were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and use was approved and monitored by the Augusta University Institutional Animal Care and Use Committee. Animals were housed under conditions of constant temperature and humidity and exposed to a 12:12-h light-dark cycle. All rats were given free access to rat chow and tap water.

At 7 weeks of age, all rats were implanted with telemetry transmitters (Data Science Inc., St. Paul, MN) according to manufacturer's specifications. Briefly, a midline incision was used to expose the abdominal aorta that was occluded to allow insertion of the transmitter catheter. The catheter was secured in place with tissue glue and the transmitter was sutured to the abdominal wall along the incision line. The skin was closed with staples that were removed a week later after the incision was healed. Animals were allowed one week to recover from surgery before being placed on receivers to obtain BP measurements. After 1 week of baseline BP recording, animals were randomized to receive either vehicle or the selective COX-2 inhibitor celecoxib for 6 weeks (from 9 to 14 weeks of age). Celecoxib was given at a dose of 10 mg/kg/day in chocolate JELL-O pudding to ensure constant delivery to each rat. This dose was shown by others to effectively inhibit COX-2 *in vivo* in rats [17,18]. Vehicle rats received pudding without drug. Rats received the pudding at the same time of day daily and all of the pudding was consumed within 5–10 min.

Rats were placed in metabolic cages (Nalgene Corp. Rochester, NY) for 24 h urine collection after one, four and six weeks of celecoxib treatment. At the end of all studies, rats were anesthetized with ketamine/xylazine (50 mg/kg and 6 mg/kg i.p., respectively; Phoenix Pharmaceuticals, St. Joseph, MO), kidneys were removed and snap-frozen in liquid nitrogen.

2.1. Urinary measurements

To determine the impact of the selective COX-2 inhibitor celecoxib on PGs production, urinary PGs metabolites were measured in vehicle and celecoxib-treated SHR via commercially available enzyme-linked immunosorbent assay (ELISA) kits (Cayman Chemical, Ann Arbor, MI). Urinary excretion rates of PGE metabolite (PGEM) were measured as an indicator of PGE_2 production. Urinary 6-keto $PGF_{1\alpha}$ excretion level, a