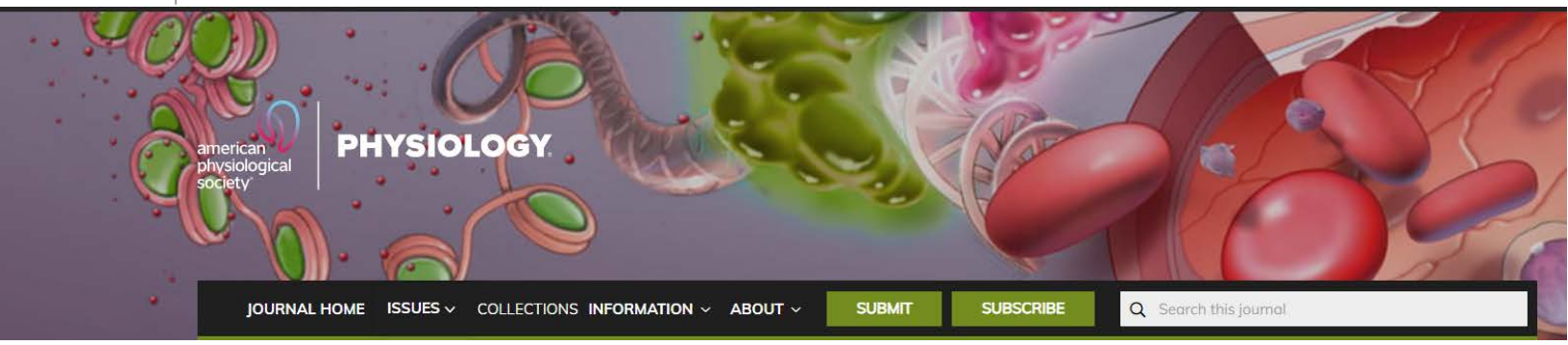

Sex differences in renal physiology and pathophysiology

Sex differences in the Biosynthesis and Metabolism of Dihydrotestosterone in the Rat Kidney

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Abstract

We recently established the presence of the estrogen biosynthesis machinery in male and female Sprague Dawley (SD) rat kidney. Given that estrogenic signaling promotes natriuresis and lowers blood pressure, sex differences in local renal estrogen production may play a critical role in sex differences in hypertension and salt handling. Androgen biosynthesis is interconnected with estrogen biosynthesis however it is not known whether the kidney is capable of biosynthesizing androgens. The goal of this study was to investigate the impact of sex and dietary salt on the biosynthesis and metabolism of dihydrotestosterone (DHT) in the rat kidney. We hypothesize that the male kidney has a greater capacity to biosynthesize DHT than females while the female kidney has a greater capacity to metabolize DHT to inactive metabolites. Given that DHT is a non-aromatizable androgen, we did not anticipate HS diet

SD rats maintained on a normal salt (NS) or high salt (HS) diet. The renal expression of several key enzymes in DHT production and metabolism were assessed via RT-qPCR (n=6-7/group). SRD5A1, which converts testosterone to DHT, surprisingly had a higher expression in females compared to males (NS; P=0.0141 HS; P=0.0006). A HS diet increased the expression of SRD5A1 in female rats (P=0.0093) (NS male; 100.0 ± 11.6 vs NS female; 297.8 ± 37.7 vs HS male 243.0 ± 39.2 vs HS female 498.8 ± 44.8 %NS male). AKR1C1, which catalyzes the conversion of DHT into 5α-androstane-3β,17β-diol (3β-diol), had greater expression in females vs males (NS; P=0.0091 HS; p<0.0001) with no diet impact (NS male; 100.0 ± 8.7 vs NS female; 502.8 ± 71.0 vs HS male; 131.6 ± 17.9 vs HS female; 770.4 ± 135.5 %NS male). AKR1C2, which catalyzes the conversion of DHT into 5α-androstane-3α,17β-diol (3α-diol), was expressed to a greater extent in females compared to males (NS; P=0.0159 HS; p<0.0001) and HS diet further increased its expression in females (P=0.0001) (NS male; 100.0 ± 19.2 vs NS female; 4,389.9 ± 707.2 vs HS male; 146.0 ± 19.6 vs HS female; 11,089.7 ± 1611.4 %NS male). HSD17B7, which catalyzes the conversion of 3α-diol back to DHT had lower expression in females vs males (NS; P=0.0200 HS; P=0.0108) with no diet effect (NS male; 100.0 ± 14.9 vs NS female; 49.6 ± 3.4 vs HS male; 99.5 ± 14.1 vs HS female; 45.0 ± 4.6 vs %NS male). The expression of Cyp7B1, which inactivates 3β-diol, was not significantly different based on sex or diet. Neither UGT2B15 nor UGT2B17, which catalyze the conversion of DHT into DHT-glucuronide, an inactive readily excretable metabolite, were impacted by sex or diet. In summary, the female kidney has a greater expression of SRD5A1, AKR1C1, and AKR1C2 and a reduced expression of HSD17B7 compared to males. Increased dietary salt intake enhances the expression of SRD5A1 and AKR1C2 only in the female kidney. This data suggests an apparent increased renal DHT production in females which is further upregulated with increased salt intake. In addition, the data suggest the female kidney has an enhanced machinery for metabolizing DHT to the metabolites 3β-diol and 3α-diol. Of note, the androgen metabolites, 3β-diol and 3α-diol, do not bind the androgen receptor, but instead have a high binding affinity for estrogen receptor ERβ. ERβ signaling has been shown to be protective against hypertension in females and thus may be a mechanism through which females have reduced hypertension prevalence. 3β-diol and 3α-diol could pose as novel avenues of

needed to understand their potential physiological role in sodium homeostasis and blood pressure control.

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