The G Protein-Coupled Estrogen Receptor (GPER-1): A Novel Regulator in the Kidney

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Gender has a crucial influence on incidence and prognosis of chronic and acute kidney diseases since women generally have a lower morbidity and mortality compared to men. Several studies have reported the capability of estrogen to promote homeostatic and protective effects in the kidney via a pregenomic mechanism that is mediated by G protein-coupled receptor 30 (GPR30), but not by classic Estrogen Receptors (ER), ERα or ERβ. GPR30 was first cloned as an orphan receptor from a Burkitt’s lymphoma cell line and then confirmed in other cell lines. Prior studies have demonstrated that GPR30 is a specific, high affinity, G-coupled estrogen membrane receptor activated by naturally occurring and synthetic estrogens and anti-estrogens including estradiol-17β, G1, tamoxifen, ICI182,780, Genestein and Bisphenol A, but not by cortisol, progesterone or testosterone in both mammals and fish. Thus, GPR30 was designated G protein-coupled estrogen receptor-1 (GPER-1) by the International Union of Pharmacology in 2007.

GPER-1 is highly expressed in kidney tissues albeit with differences regarding its subcellular distribution, which may in part be due to differences in methodological approaches in measuring its expression and activity. Recently, Filardo and coworkers evaluated the topographic mapping of GPER-1 expression in renal tubules using dual immunostaining of the receptors and specific markers for distinct tubules in tissue section. The results revealed that GPER-1 immunoreactivity is mainly localized in the distal convoluted tubules and the loop of Henle, and to a lower level in the proximal convoluted tubules. Interestingly, the subcellular distribution pattern of GPER-1 in these tubules is distinct: GPER-1 in the distal convoluted tubules and the loop of Henle mainly resides in the cytoplasm with less GPER-1 in the basolateral plasma membrane, whereas GPER-1 in the proximal convoluted tubules is primarily located in the basolateral membrane. Similar pattern for GPER-1 expression has been observed in male rat renal epithelia. Intriguingly, subcellular distribution of GPER-1 is modulated during the estrus cycle. During the secretory phases of the estrus cycle, GPER-1 is upregulated on cortical epithelia and localized to the basolateral surface during proestrus and redistributed intracellularly during estrus. GPER-1 is down-modulated during luteal phases of the estrus cycle with significantly less receptors on the surface of renal epithelia. Lindsey and colleagues reported that GPER-1 immunoreactivity is predominantly localized to the apical surface of the proximal tubule and minimally to the glomerulus but not to the distal tubules in female hypertensive rat. Differences in the subcellular distribution pattern and topographic localization of GPER-1 in distinct renal tubules may suggest that GPER-1 plays differential roles in mediating fluid and electrolyte homeostasis, and that pathological conditions such as hypertension may influence subcellular translocation of GPER-1 in renal epithelia.
context of physiological and pathological conditions. The specific GPER-1 agonist, G1, estradiol-17β (E2), and ICI 182,780 (the ER antagonist and GPER-1 agonist) have been reported to increase acute Ca²⁺ concentration and H⁺-ATPase activity intracellular calcium signals in microdissected renal tubule segments and isolated intercalated cells but not in similar explants and cell cultures isolated from GPER-1–deleted mice, suggesting a role for GPER-1 in regulating Na⁺ and Ca²⁺ reabsorption in renal tubules and subsequently affecting fluid retention. Prior studies revealed that G1 and estradiol-17β induce vasodilation in female mouse, pig and rat and vasoconstriction in male rat. A recent study demonstrated that GPER-1 exerts beneficial effects on preventing excessive mesangial matrix production and modulates mesangial cell migration. Chappell and co-workers have shown that GPER-1 colocalizes with megalin in renal proximal tubules and that G1 ameliorates salt-induced renal injury in female mRen2. Lewis mice independently of changes in systolic blood pressure. Estrogen has been shown to ameliorates ischemic glomerular endothelial hyperpermeability via a GPER-1–mediated mechanism.

Collectively, while more work is required to elucidate the physiological significance of GPER-1 modulation in the kidney, current findings strongly suggest that GPER-1 in the kidney facilitates selective reabsorption of water and electrolytes, mediates renal vascular activities and mesangial cell behavior and reduces proteinuria and oxidative stress.

CONFLICTS OF INTEREST: None.

REFERENCES


