NEPHROLOGY

Openventio PUBLISHERS

ISSN 2380-0445 Open Journal http://dx.doi.org/10.17140/NPOJ-1-e002

Editorial

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Volume 1 : Issue 1
Article Ref. #: 1000NPOJ1e002

Article History
Received: April 16th, 2015
Accepted: April 16th, 2015
Published: April 17th, 2015

Citation
Liu Z, Liu N, Cheng S. The G protein-coupled estrogen receptor (GPER-1): a novel regulator in the kidney. *Nephrol Open J*. 2015; 1(1): e4-e6. doi: 10.17140/NPOJ-1-e002

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.[1,2] 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.[2] GPR30 was first cloned as an orphan receptor from a Burkitt's lymphoma cell line[3] and then confirmed in other cell lines.[4] Prior studies have demonstrated that GPR30 is a specific, high affinity, G_s-coupled estrogen membrane receptor activated by naturally occurring and synthetic estrogens and antiestrogens including estradiol-17β, G1, tamoxifen, ICI182,780, Genestein and Bisphenol A, but not by cortisol, progesterone or testosterone in both mammals and fish.[5-15] Thus, GPR30 was designated G protein-coupled estrogen receptor-1 (GPER-1) by the International Union of Pharmacology in 2007.[16]

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.[17-21] 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.[22] 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.[22] 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.[22] Similar pattern for GPER-1 expression has been observed in male rat renal epithelia.[19] 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.[22] Lindsey and colleagues reported that GPER-1 imunoreactivity 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.[20] 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.

Accumulating evidence has shown multiple roles for GPER-1 in the kidney in the

context of physiological and pathological conditions. The specific GPER-1 agonist, G1,[15] estradiol-17β (E2), and ICI 182,780 (the ER antagonist and GPER-1 agonist)[12] have been reported to increase acute Ca^{2+} 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 Ca^{2+} reabsorption in renal tubules and subsequently affecting fluid retention.[21] Prior studies revealed that G1 and estradiol-17β induce vasodilation in female mouse, pig and rat and vasoconstriction in male rat.[23] A recent study demonstrated that GPER-1 exerts beneficial effects on preventing excessive mesangial matrix production and modulates mesangial cell migration.[2] 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.[20] Estrogen has been shown to ameliorateischemic glomerular endothelial hyperpermeability *via* a GPER-1-mediated mechanism.[1]

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.

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