Published in final edited form as:

Curr Opin Nephrol Hypertens. 2014 September ; 23(5): 507–512. doi:10.1097/MNH.0000000000000048.

“Extra” sensory Perception: The Role of Gpr Receptors in the Kidney

Jennifer L. Pluznick¹

¹Dept. of Physiology, Johns Hopkins University School of Medicine, Baltimore, MD 21205 (410) 614-4660 (phone), (410) 955-0461 (fax)

Abstract

Purpose of review—This review will summarize recent literature highlighting the roles of sensory Gpr receptors and their roles in renal function.

Recent findings—Chemoreceptors play important roles in renal physiology where they modulate renal function in response to ligands from a variety of sources.

Summary—As specialized chemical detectors, chemoreceptors in the kidney function to monitor the level of a variety of chemical ligands in the body, and to adjust renal function accordingly. In addition to olfactory receptors and taste receptors, G-protein coupled receptors of the orphan Gpr family are now being found to play a ‘sensory’ role in renal physiology. Identifying the physiological roles of these receptors, and elucidating the cell biology underlying these signaling pathways, can give us novel insights into renal function.

Keywords

renal; kidney; chemoreceptor; ORs; olfactory receptor

INTRODUCTION

The kidney continually monitors a wide variety of substances in the plasma and the forming urine in order to regulate the homeostatic balance of endogenous substances, as well as to promote the excretion of toxins. The pivotal role of the kidney in the maintenance of whole-body homeostasis is revealed in the pathophysiology of renal failure, in which key parameters of homeostasis are disrupted including plasma levels of sodium, potassium, calcium, phosphate, and pH, as well as defects in red blood cell number and extracellular fluid volume. In order to function properly, the kidney must be able to accurately monitor of the concentrations of a wide range of substances. To do this, the kidney employs a number of strategies, including one which has become recognized only recently: the role of “sensory” receptors.

Recent studies have highlighted roles that sensory receptors -taste receptors, olfactory receptors, and G-protein coupled receptors of the orphan “GPR” family – play in a variety of

Correspondence to: Jennifer L. Pluznick.

Conflicts of interest: No conflicts of interest.

tissues throughout the body. The ligands for these receptors are often chemicals already known to be essential to physiology [1;2], indicating that substances such as metabolites may serve signaling functions beyond their traditional roles [3–5]. For example, the PKD2L1/PKD1L3 complex is a pH sensor which is found both in the tongue and in the spinal column, and although it serves to sense pH in both environments, in the tongue it functions as the sour taste receptor - and in the spinal column it acts to monitor the pH of the cerebrospinal fluid [6]. Similarly, the bitter taste receptors found in the tongue are also present in the ciliated epithelium of the lung, where they mediate bronchodilation and changes in ciliary beat frequency in response to inhaled receptor ligands [7;8]. Likewise, sweet taste receptors play a role in the gut, where they regulate glucose transport and neuroendocrine secretion [9;10]. In addition to taste receptors, olfactory receptors also play important roles in mediating chemosensing in muscle [11] and sperm [12], and recently we have reported that olfactory receptors also play a role in the kidney and cardiovascular system [13;14] (reviewed in [15] and [16]).

In addition to taste receptors and olfactory receptors, orphan receptors of the “GPR” family (a subset of the GPCR superfamily “Class A”) are another large class of receptors which can serve ‘sensory’ functions. The Gpr receptors are orphan receptors with no known ligands – however, some recent studies have begun to deorphanize these receptors and delineate their functions, and it is becoming clear that these receptors play diverse roles in physiology in a wide variety of tissues. For example, Gpr30 acts as an estrogen receptor and plays a role in breast cancer [17;18], Gpr37 and Gpr37L1 are receptors for prosaptide which mediate protection against oxidative stress in astrocytes [19], and Gpr56 is thought to play a role in cancer progression [20]. In addition, a subset of the Gpr’s have been found to play a role in sensing compounds related to metabolism [21], including short chain fatty acids (Gpr41 [22–26], Gpr43 [22–24]), medium chain fatty acids (Gpr84, [21;27]), and long chain fatty acids (Gpr40 [24;28–30]; Gpr119, [21;31]; Gpr120 [29]). Not surprisingly, many of these fatty acid-sensing Gpr’s play roles in metabolism in a variety of tissues (including the pancreas, central nervous system, gastrointestinal system, adipose tissue, and leukocytes and keratinocytes [21]), and are being studied in the context of type 2 diabetes [28–31] as well as inflammation [24;27;32].

It is impressive to note that when receptor expression is assayed in an unbiased fashion, the Gpr receptors are often found to be quite highly expressed [33]. In contrast, however, the Gpr family is relatively understudied, due in large part to the fact that most Gpr receptors are orphans. Although one must appreciate the risk and difficulty of exploring the roles of receptors whose ligands and signaling pathways are unknown, it is unlikely that these receptors are well-expressed in specific tissues without a purpose or function. Thus, it is both informative and necessary to begin to understand the roles of these novel receptors and pathways, and to expand the current repertoire of receptors studied in the kidney beyond the ‘usual suspects.’ It is our hope that by studying these receptors, we can gain novel and unexpected insights into renal physiology – indeed, recent studies have begun to greatly expand our knowledge in this area. In this review, we will highlight studies which have delineated exciting and novel roles for Gpr receptors in the kidney.

Gpr30 (GPER1)

Gpr30 (also known as GPER1, or G-protein coupled estrogen receptor 1) is an estrogen receptor which is thought to play a role in a subset of breast cancers [17;18]. However, it has also been suggested that estrogen-Gpr30 interacts with the renin-angiotension-aldosterone system (RAAS) as well as nitric oxide signaling (NOS) to influence renal and cardiovascular physiology [34]. Furthermore, in studies beginning in ~2011, accumulating evidence suggests that Gpr30 functions as a receptor for aldosterone in the vascular endothelium [35–39], although there are dissenting reports to this view (summarized in [40]). Although aldosterone is a steroid receptor, it has long been appreciated that this hormone also exhibits ‘nongenomic’ effects not attributable to its canonical nuclear receptor [41]. At least some of these vascular effects may in fact be mediated by Gpr30, although, as stated above, the data is not yet definitive.

With regards to the kidney specifically, a study by Hofmeister, et al in 2012 [42] demonstrated that Gpr30 mediates the actions of estrogen in intercalated cells in isolated renal tubules. Estrogen, like aldosterone, is a steroid hormone which has also been appreciated to have ‘non-genomic’ effects. In these studies, the authors first demonstrated that Gpr30 mRNA is present in isolated murine DCT2/CNT/iCCD segments (distal convoluted tubule 2/connecting tubule/initial cortical collecting duct). The authors then showed that estrogen caused an increase in intracellular calcium in intercalated cells in these tubules, and that this effect was absent in tubules from Gpr30 knockout (KO) mice. In future studies, it will be important to determine if Gpr30 – or other orphaned Gprs – may also be responsible for some of the ‘non-genomic’ effects of aldosterone in the kidney as well.

Gpr41

Gpr41 and Gpr43 were identified as receptors for short chain fatty acids (SCFAs) by two different groups in 2003 [22;23]; in addition, another GPCR (Olfr78[14]) has a similar ligand profile. Intriguingly, the primary source of SCFAs in the plasma is the gut microbiota [43]. SCFAs produced by microbiota metabolism interact with host receptors in order to modulate host physiology (for example, host adiposity via Gpr41 activation [25]).

Recently, Gpr41 was found to be expressed in the kidney and in blood vessels of the cardiovascular system by RT-PCR [14] – in addition, the two other SCFA receptors (Gpr43 and Olfr78) were also expressed in the kidney and cardiovascular system. It was reported that in wild-type mice, an intravenous dose of propionate produced a decrease in BP (13.9 mmHg [14]). However, this decrease was absent in Gpr41^{-/-}. These data indicate that Gpr41 mediates the hypotensive effects of propionate (thought to be due to changes in vascular resistance in the peripheral vasculature). In addition, it was found that this effect is also opposed by another SCFA receptor (Olfr78) [14;16]. This study concluded that SCFAs interacted with these SCFA receptors to modulate host blood pressure, and that the bulk of the hypotensive response to propionate is mediated by Gpr41 (although Olfr78, and possibly Gpr43, also play roles to modulate the response). As described above, Gpr41 is also found in the kidney by RT-PCR in addition to expression in the cardiovascular system (as is Gpr43 and Olfr78). Although Olfr78 was localized to the renal afferent arteriole [14] and reported to have a role in modulating renin release, the specific renal cell type where Gpr41/Gpr43

are localized has not yet been elucidated (although Gpr41 -along with Gpr43 and Olfr78 - were expressed in isolated juxtaglomeruli apparatus). In future studies, it will be important to precisely localize Gpr41 and Gpr43 within the kidney, and determine how these different SCFA receptors interact to modulate host blood pressure responses.

Gpr48 (Lgr4)

The most extensively studied renal Gpr is Gpr48, also referred to as Lgr4. Gpr48 tissue distribution has been examined by three different groups, using a variety of techniques including northern blot [44], murine gene trap [45] and the use of a monoclonal antibody in both human and mouse tissues [46]. All three groups agree that, in addition to other tissues, Gpr48 is expressed in the kidney. In particular, Gpr48 localizes to the proximal and distal tubules, but not glomeruli [45;46], with a greater abundance in the cortex than in the medulla [45]. In 2011, three groups independently reported that Gpr48 (Lgr4) and its relative Lgr5 are receptors for R-spondins [47–49], which are wnt signaling agonists.

Several studies have implicated Gpr48 in renal development, and two different whole-animal KO mice have been used to study Gpr48 in the kidney. Using the first KO model, it was reported that Gpr48KO animals are born in lower than expected frequencies, and those animals which do survive to birth typically die by P2 with renal hypoplasia and elevated plasma creatinine [50]. (Interestingly, Gpr48 mice do not appear to nurse [50], which likely contributes to neonatal death, and may be related to the expression of Gpr48 in the OE and VNO [45], as nursing at birth is olfactory dependent [51;52].) The authors also found that the ureteric bud (UB) in these animals undergoes premature differentiation, as evidenced by the premature expression of DBA and AQP3 in the UB of Gpr48KO mice at E15.5. This study was performed using mice on a mixed background; subsequently, the authors backcrossed the mice onto C57BL/6J, and reported that on this background, the phenotype was even more severe: no Gpr48KO pups survived to birth [53], and renal hypoplasia was evident in embryonic pups (E16.5). The authors looked at Gpr48 expression during embryogenesis using *in situ* hybridization, and found that Gpr48 is expressed in renal vesicles and in progenitors of the tubule epithelium (including comma-shaped and S-shaped bodies), and that Gpr48KO mice exhibit impaired branching morphogenesis. In another follow-up study [54], it was reported that apoptosis is increased in Gpr48KO kidneys, and that the expression the anti-apoptotic PAX2 is decreased. The authors suggest that an increase in apoptosis likely contributes to the renal hypoplasia seen in Gpr48 KO animals.

In the original study examining the role of Gpr48 in renal development, it was found that one single Gpr48KO mouse lived beyond P2, and survived until P42. At death, this animal was found to have multiple, fluid-filled renal cysts (among other pathological findings) [50]. In agreement with this, another group reported that genetic deletion of Gpr48 induces renal cystic disease [55]. For these studies, the authors used a different Gpr48 KO [55], which also has significant perinatal death (~60% of pups died between P0–P1). However, in this case the authors were able to generate Gpr48KO mice which were spared embryonic or neonatal death through breeding and crossbreeding. In these mice, they found that the kidney weight/body weight (KW/BW) ratios were consistently lower in Gpr48KO animals. Typically, one would expect animals with renal cystic disease to have a higher KW/BW,

however, presumably renal hypoplasia in these animals (reported in the other KO model) results in a lower KW/BW ratio despite the apparent cystic burden. In sum, 67% of the Gpr48KO mice developed multiple renal cysts. Further analysis showed that both polycystin 1 (PC1) and polycystin 2 (PC2) expression was reduced in Gpr48 animals (PC1/PC2 being the genes mutated in autosomal dominant polycystic kidney disease, or ADPKD). In addition, β -catenin/wnt signaling (which has been implicated in PKD[56]) was elevated in Gpr48 knockout animals, indicating that the cysts seen in the Gpr48KO may be contributed to by alterations in PC1/PC2, as well as alterations in wnt/ β -catenin signaling.

Finally, Gpr48 has also been linked to expression of the mineralocorticoid receptor (MR) [57]. These studies were done using the second Gpr48 knockout described above; although ~50% of the KO mice died by P2 in this study, the authors were able to study the remaining KO animals. When fed a low salt diet, these mice were found to have a phenotype akin to a mild form of pseudohypoaldosteronism type I, including hyponatremia with salt loss and hyperkalemia, despite increased aldosterone (a milder phenotype was seen when mice were given normal sodium chow). In addition, Gpr48KO animals expressed lower levels of α ENAC and the Na^+/K^+ ATPase, as well as lower levels of MR. The authors went on to demonstrate that Gpr48 regulates MR expression, and suggest that Gpr48 may be necessary for normal expression levels of MR. In support of this, in 2013 it was reported [58] that a nonsense mutation in Gpr48 in humans is associated with hyperkalemia and hyponatremia (among a variety of other phenotypes; no other renal phenotypes were reported).

Gpr91

Gpr91 was initially identified a receptor for succinate in 2004 [59]. Succinate is an intermediate of the citric acid cycle, and as such is intimately woven into energy usage and metabolism. Although chiefly found in the mitochondria, succinate is also found in the plasma in the μM range [3]. In addition, there are physiological conditions (hypoxia, oxidative stress) under which succinate levels rise [60;61].

In the initial paper in 2004, He, et al reported the unexpected finding that succinate induces a hypertensive response in animals, which is Gpr91-dependent [3;62]. This blood pressure effect is mediated by the renin-angiotensin system, and [3] further studies demonstrated that this hypertension is caused by an increase in renin release, mediated by succinate activation of Gpr91 in the macula densa [63][5]. These data imply that succinate ‘sensing’ may allow the kidney to monitor for signs of renal energy deprivation, and to increase blood pressure (and renal perfusion) when these conditions occur.

Intriguingly, this previously unrecognized signaling pathway has now been found to play roles not only in physiology, but in pathophysiology as well. High plasma glucose levels cause local increases in succinate levels which can promote renin release via Gpr91 [60;64]. It is known that metabolic syndrome is often associated with the development of hypertension; these data provide a potential explanation for why increased plasma glucose levels may lead to hypertension. Along the same lines, it may be possible to utilize succinate as a biomarker for potential to progress to diabetic nephropathy; indeed, succinate levels are elevated in the urine of diabetic mice [64].

CONCLUSION

In summary, sensory receptors play a variety of important roles in traditionally ‘non-sensory’ organs. Recently, studies have outlined a number of novel roles for Gpr receptors in a variety of pathways in the kidney. In the future, it will be important to not only further investigate the functions of these receptors, but to discover the full complement of Gpr receptors in the kidney and their functional roles.

Acknowledgments

This work was supported a Carl W. Gottschalk Award from the American Society of Nephrology.

The author would like to thank members of the Pluznick Lab for helpful discussions, and the NIH (R00-DK081610) and ASN (Gottschalk) for funding support.

Reference List

1. Huang AL, Chen X, Hoon MA, et al. The cells and logic for mammalian sour taste detection. *Nature*. 2006; 442:934–938. [PubMed: 16929298]
2. Magistroni R, Furci L, Albertazzi A. Autosomal dominant polycystic kidney disease: from genes to cilium. *G Ital Nefrol*. 2008; 25:183–191. [PubMed: 18350498]
3. He W, Miao FJ, Lin DC, et al. Citric acid cycle intermediates as ligands for orphan G-protein-coupled receptors. *Nature*. 2004; 429:188–193. [PubMed: 15141213]
4. Kimura I, Inoue D, Maeda T, et al. Short-chain fatty acids and ketones directly regulate sympathetic nervous system via G protein-coupled receptor 41 (GPR41). *Proc Natl Acad Sci USA*. 2011; 108:8030–8035. [PubMed: 21518883]
5. Vargas SL, Toma I, Kang JJ, et al. Activation of the succinate receptor GPR91 in macula densa cells causes renin release. *J Am Soc Nephrol*. 2009; 20:1002–1011. [PubMed: 19389848]
6. Huang AL, Chen X, Hoon MA, et al. The cells and logic for mammalian sour taste detection. *Nature*. 2006; 442:934–938. [PubMed: 16929298]
7. Deshpande DA, Wang WC, McIlmoyle EL, et al. Bitter taste receptors on airway smooth muscle bronchodilate by localized calcium signaling and reverse obstruction. *Nat Med*. 2010; 16:1299–1304. [PubMed: 20972434]
8. Shah AS, Ben-Shahar Y, Moninger TO, et al. Motile cilia of human airway epithelia are chemosensory. *Science*. 2009; 325:1131–1134. [PubMed: 19628819]
9. Jang HJ, Kokrashvili Z, Theodorakis MJ, et al. Gut-expressed gustducin and taste receptors regulate secretion of glucagon-like peptide-1. *Proc Natl Acad Sci USA*. 2007; 104:15069–15074. [PubMed: 17724330]
10. Margolskee RF, Dyer J, Kokrashvili Z, et al. T1R3 and gustducin in gut sense sugars to regulate expression of Na⁺-glucose cotransporter 1. *Proc Natl Acad Sci USA*. 2007; 104:15075–15080. [PubMed: 17724332]
11. Griffin CA, Kafadar KA, Pavlath GK. MOR23 promotes muscle regeneration and regulates cell adhesion and migration. *Dev Cell*. 2009; 17:649–661. [PubMed: 19922870]
12. Spehr M, Gisselmann G, Poplawski A, et al. Identification of a testicular odorant receptor mediating human sperm chemotaxis. *Science*. 2003; 299:2054–2058. [PubMed: 12663925]
13. Pluznick JL, Zou DJ, Zhang X, et al. Functional expression of the olfactory signaling system in the kidney. *Proc Natl Acad Sci USA*. 2009; 106:2059–2064. [PubMed: 19174512]
- 14*. Pluznick JL, Protzko RJ, Gevorgyan H, et al. Olfactory receptor responding to gut microbiota-derived signals plays a role in renin secretion and blood pressure regulation. *Proc Natl Acad Sci USA*. 2013; 110:4410–4415. This study showed that three different short chain fatty acid (SCFA) receptors are expressed in the kidney and cardiovascular system, and that they play a role in blood pressure modulation. [PubMed: 23401498]

15. Pluznick JL, Caplan MJ. Novel sensory signaling systems in the kidney. *Curr Opin Nephrol Hypertens*. 2012
16. Pluznick JL. Renal and cardiovascular sensory receptors and blood pressure regulation. *Am J Physiol Renal Physiol*. 2013; 305:F439–F444. [PubMed: 23761671]
17. Srivastava DP, Evans PD. G-protein oestrogen receptor 1: trials and tribulations of a membrane oestrogen receptor. *J Neuroendocrinol*. 2013; 25:1219–1230. [PubMed: 23822769]
18. Steiman J, Peralta EA, Louis S, Kamel O. Biology of the estrogen receptor, GPR30, in triple negative breast cancer. *Am J Surg*. 2013; 206:698–703. [PubMed: 24011568]
19. Meyer RC, Giddens MM, Schaefer SA, Hall RA. GPR37 and GPR37L1 are receptors for the neuroprotective and glioprotective factors prosaptide and prosaposin. *Proc Natl Acad Sci USA*. 2013; 110:9529–9534. [PubMed: 23690594]
20. Yang L, Xu L. GPR56 in cancer progression: current status and future perspective. *Future Oncol*. 2012; 8:431–440. [PubMed: 22515446]
21. Vinolo MA, Hirabara SM, Curi R. G-protein-coupled receptors as fat sensors. *Curr Opin Clin Nutr Metab Care*. 2012; 15:112–116. [PubMed: 22234165]
22. Brown AJ, Goldsworthy SM, Barnes AA, et al. The Orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids. *J Biol Chem*. 2003; 278:11312–11319. [PubMed: 12496283]
23. Le PE, Loison C, Struyf S, et al. Functional characterization of human receptors for short chain fatty acids and their role in polymorphonuclear cell activation. *J Biol Chem*. 2003; 278:25481–25489. [PubMed: 12711604]
24. Oh DY, Lagakos WS. The role of G-protein-coupled receptors in mediating the effect of fatty acids on inflammation and insulin sensitivity. *Curr Opin Clin Nutr Metab Care*. 2011; 14:322–327. [PubMed: 21587066]
25. Samuel BS, Shaito A, Motoike T, et al. Effects of the gut microbiota on host adiposity are modulated by the short-chain fatty-acid binding G protein-coupled receptor, Gpr41. *Proc Natl Acad Sci USA*. 2008; 105:16767–16772. [PubMed: 18931303]
26. Bellahcene M, O'Dowd JF, Wargent ET, et al. Male mice that lack the G-protein-coupled receptor GPR41 have low energy expenditure and increased body fat content. *Br J Nutr*. 2013; 109:1755–1764. [PubMed: 23110765]
27. Suzuki M, Takaishi S, Nagasaki M, et al. Medium-chain fatty acid-sensing receptor, GPR84, is a proinflammatory receptor. *J Biol Chem*. 2013; 288:10684–10691. [PubMed: 23449982]
28. Mancini AD, Poirout V. The fatty acid receptor FFA1/GPR40 a decade later: how much do we know? *Trends Endocrinol Metab*. 2013; 24:398–407. [PubMed: 23631851]
29. Halder S, Kumar S, Sharma R. The therapeutic potential of GPR120: a patent review. *Expert Opin Ther Pat*. 2013; 23:1581–1590. [PubMed: 24094095]
30. Burant CF. Activation of GPR40 as a therapeutic target for the treatment of type 2 diabetes. *Diabetes Care*. 2013; 36 (Suppl 2):S175–S179. [PubMed: 23882043]
31. Hansen HS, Rosenkilde MM, Holst JJ, Schwartz TW. GPR119 as a fat sensor. *Trends Pharmacol Sci*. 2012; 33:374–381. [PubMed: 22560300]
32. Maslowski KM, Vieira AT, Ng A, et al. Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. *Nature*. 2009; 461:1282–1286. [PubMed: 19865172]
33. Snead AN, Insel PA. Defining the cellular repertoire of GPCRs identifies a profibrotic role for the most highly expressed receptor, protease-activated receptor 1, in cardiac fibroblasts. *FASEB J*. 2012; 26:4540–4547. [PubMed: 22859370]
34. Zhao Z, Wang H, Jessup JA, et al. Role of estrogen in diastolic dysfunction. *Am J Physiol Heart Circ Physiol*. 2014; 306:H628–H640. [PubMed: 24414072]
35. Gros R, Ding Q, Liu B, et al. Aldosterone mediates its rapid effects in vascular endothelial cells through GPER activation. *Am J Physiol Cell Physiol*. 2013; 304:C532–C540. [PubMed: 23283935]
36. Briet M, Schiffrin EL. Vascular actions of aldosterone. *J Vasc Res*. 2013; 50:89–99. [PubMed: 23172373]

37. Feldman RD, Gros R. Unraveling the mechanisms underlying the rapid vascular effects of steroids: sorting out the receptors and the pathways. *Br J Pharmacol.* 2011; 163:1163–1169. [PubMed: 21545416]
38. Wendler A, Wehling M. Is GPR30 the membrane aldosterone receptor postulated 20 years ago? *Hypertension.* 2011; 57:e16. [PubMed: 21422381]
39. Gros R, Ding Q, Sklar LA, et al. GPR30 expression is required for the mineralocorticoid receptor-independent rapid vascular effects of aldosterone. *Hypertension.* 2011; 57:442–451. [PubMed: 21242460]
40. Barton M. Position paper: The membrane estrogen receptor GPER--Clues and questions. *Steroids.* 2012; 77:935–942. [PubMed: 22521564]
41. Wehling M, Kasmayr J, Theisen K. Rapid effects of mineralocorticoids on sodium-proton exchanger: genomic or nongenomic pathway? *Am J Physiol.* 1991; 260:E719–E726. [PubMed: 1852112]
- 42*. Hofmeister MV, Damkier HH, Christensen BM, et al. 17beta-Estradiol induces nongenomic effects in renal intercalated cells through G protein-coupled estrogen receptor 1. *Am J Physiol Renal Physiol.* 2012; 302:F358–F368. This study showed that Gpr30 (estrogen receptor) mediates nongenomic effects of estrogen to alter calcium signaling and H⁺-ATPase activity intercalated cells. [PubMed: 21993891]
43. Bugaut M. Occurrence, absorption and metabolism of short chain fatty acids in the digestive tract of mammals. *Comp Biochem Physiol B.* 1987; 86:439–472. [PubMed: 3297476]
44. Loh ED, Broussard SR, Kolakowski LF. Molecular characterization of a novel glycoprotein hormone G-protein-coupled receptor. *Biochem Biophys Res Commun.* 2001; 282:757–764. [PubMed: 11401528]
45. Van SG, Mendive F, Pochet R, Vassart G. Expression pattern of the orphan receptor LGR4/GPR48 gene in the mouse. *Histochem Cell Biol.* 2005; 124:35–50. [PubMed: 16028069]
46. Yi J, Xiong W, Gong X, et al. Analysis of LGR4 receptor distribution in human and mouse tissues. *PLoS One.* 2013; 8:e78144. [PubMed: 24205130]
47. Glinka A, Dolde C, Kirsch N, et al. LGR4 and LGR5 are R-spondin receptors mediating Wnt/beta-catenin and Wnt/PCP signalling. *EMBO Rep.* 2011; 12:1055–1061. [PubMed: 21909076]
48. de LW, Barker N, Low TY, et al. Lgr5 homologues associate with Wnt receptors and mediate R-spondin signalling. *Nature.* 2011; 476:293–297. [PubMed: 21727895]
49. Carmon KS, Gong X, Lin Q, et al. R-spondins function as ligands of the orphan receptors LGR4 and LGR5 to regulate Wnt/beta-catenin signaling. *Proc Natl Acad Sci USA.* 2011; 108:11452–11457. [PubMed: 21693646]
50. Kato S, Matsubara M, Matsuo T, et al. Leucine-rich repeat-containing G protein-coupled receptor-4 (LGR4, Gpr48) is essential for renal development in mice. *Nephron Exp Nephrol.* 2006; 104:e63–e75. [PubMed: 16785743]
51. Belluscio L, Gold GH, Nemes A, Axel R. Mice deficient in G(olf) are anosmic. *Neuron.* 1998; 20:69–81. [PubMed: 9459443]
52. Wong ST, Trinh K, Hacker B, et al. Disruption of the type III adenylyl cyclase gene leads to peripheral and behavioral anosmia in transgenic mice. *Neuron.* 2000; 27:487–497. [PubMed: 11055432]
53. Mohri Y, Oyama K, Akamatsu A, et al. Lgr4-deficient mice showed premature differentiation of ureteric bud with reduced expression of Wnt effector Lef1 and Gata3. *Dev Dyn.* 2011; 240:1626–1634. [PubMed: 21523854]
54. Mohri Y, Oyama K, Sone M, et al. LGR4 is required for the cell survival of the peripheral mesenchyme at the embryonic stages of nephrogenesis. *Biosci Biotechnol Biochem.* 2012; 76:888–891. [PubMed: 22738954]
- 55*. Dang Y, Liu B, Xu P, et al. Gpr48 deficiency induces polycystic kidney lesions and renal fibrosis in mice by activating wnt signal pathway. *PLoS One.* 2014; 9:e89835. In this study, Gpr48 null mice were shown to have a renal cystic phenotype in addition to the renal hypoplasia phenotype. [PubMed: 24595031]
56. Lal M, Song X, Pluznick JL, et al. Polycystin-1 C-terminal tail associates with beta-catenin and inhibits canonical Wnt signaling. *Hum Mol Genet.* 2008; 17:3105–3117. [PubMed: 18632682]

- 57*. Wang J, Li X, Ke Y, et al. GPR48 increases mineralocorticoid receptor gene expression. *J Am Soc Nephrol*. 2012; 23:281–293. This study demonstrated that Gpr48 null mice have a lowered expression of the mineralocorticoid receptor, and thus have a phenotype reminiscent of pseudohypoaldosteronism type I. [PubMed: 22135314]
- 58**. Styrkarsdottir U, Thorleifsson G, Sulem P, et al. Nonsense mutation in the LGR4 gene is associated with several human diseases and other traits. *Nature*. 2013; 497:517–520. In this study, the authors performed a genome wide association study looking for individuals with abnormally low bone mineral density in an Icelandic population. They discovered a rare nonsense mutation in Gpr48 which results in not only low bone mineral density, but also is associated with a variety of other phenotypes including hyperkalemia and hyponatremia, supporting a role for Gpr48 in mineralocorticoid receptor function. [PubMed: 23644456]
59. He W, Miao FJ, Lin DC, et al. Citric acid cycle intermediates as ligands for orphan G-protein-coupled receptors. *Nature*. 2004; 429:188–193. [PubMed: 15141213]
60. Peti-Peterdi J. High glucose and renin release: the role of succinate and GPR91. *Kidney Int*. 2010; 78:1214–1217. [PubMed: 20861827]
61. Goldberg ND, Passonneau JV, Lowry OH. Effects of changes in brain metabolism on the levels of citric acid cycle intermediates. *J Biol Chem*. 1966; 241:3997–4003. [PubMed: 5922095]
62. Hebert SC. Physiology: orphan detectors of metabolism. *Nature*. 2004; 429:143–145. [PubMed: 15141197]
63. Robben JH, Fenton RA, Vargas SL, et al. Localization of the succinate receptor in the distal nephron and its signaling in polarized MDCK cells. *Kidney Int*. 2009; 76:1258–1267. [PubMed: 19776718]
64. Toma I, Kang JJ, Sipos A, et al. Succinate receptor GPR91 provides a direct link between high glucose levels and renin release in murine and rabbit kidney. *J Clin Invest*. 2008; 118:2526–2534. [PubMed: 18535668]

Key Points

- Gpr receptors are orphan receptors which are relatively understudied, but are being found to play important roles in a variety of tissues.
- In the kidney, Gpr30 mediates nongenomic actions of estrogen in intercalated cells; Gpr30 has also been implicated in mediating nongenomic effects of aldosterone in the vasculature.
- Gpr41 is a short chain fatty acid receptor which plays a role in blood pressure control.
- Gpr48, also known as Lgr4, plays a role in renal development and also modulates the expression of the mineralocorticoid receptor.
- Gpr91 is a succinate receptor which plays a role in blood pressure control.