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Unsung Renal Receptors: Orphan G-protein coupled receptors play essential roles in renal development and homeostasis

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Abstract

Recent studies have shown that orphan GPCRs of the GPR family are utilized as specialized chemosensors in various tissues to detect metabolites, and in turn to activate downstream pathways which regulate systemic homeostasis. These studies often find that such metabolites are generated by well-known metabolic pathways, implying that known metabolites and chemicals may perform novel functions. In this review, we summarize recent findings highlighting the role of deorphanized GPRs in renal development and function. Understanding the role of these receptors is critical in gaining insights into mechanisms that regulate renal function both in health and in disease.

Keywords

Orphan GPCRs; Ligands; Function; Kidney

Introduction

Recent studies have highlighted the key roles that classical sensory receptors, such as olfactory receptors and taste receptors, play in whole-body physiology. Although a role for these sensory receptors outside of the nose and tongue did not begin to emerge until ~2003 (Spehr et al., 2003), it is now well appreciated that both olfactory and taste receptors are expressed in a variety of other tissues, where they act as sensitive and selective chemoreceptors to influence physiological processes (Feldmesser et al., 2006, Griffin et al., 2009, Huang et al., 2006, Spehr et al., 2003, Pluznick et al., 2009, Pluznick et al., 2013, Pluznick and Caplan, 2012, Pluznick, 2013, Shah et al., 2009, Busse et al., 2014, Kang and Koo, 2012, Kang et al., 2015, Kim et al., 2015, Bryksin and Matsumura, 2010, Wu et al., 2015). For example, the sour taste receptor also functions as a pH sensor in the spinal column (Huang et al., 2006), sweet taste receptors are expressed in the gut (Dyer et al., 2005) and may be dysregulated in diabetes (Young et al., 2013), and olfactory receptors play physiological roles in diverse tissues including the lungs (Shah et al., 2009), kidneys (Pluznick et al., 2009, Pluznick et al., 2013), and muscle (Griffin et al., 2009). Thus, although a role for olfactory and taste receptors in peripheral tissues is a nascent field, it is

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becoming clear that olfactory and taste receptors function in a variety of ways beyond their ‘classic’ roles in taste and smell.

Although physiological roles for sensory receptors (olfactory and taste) which are ‘ectopically’ expressed have been understudied until quite recently, the new and exciting functions outlined in the past ~13 years highlight the fact that we have much to learn from these ‘understudied’ receptors. However, there is another class of sensory chemoreceptors which is arguably even less studied: G-protein coupled receptors of the “Gpr” family. These receptors are a subset of the GPCR superfamily Class A, and were all named with the prefix “Gpr” (for G-protein (coupled) receptor) because at the time that they were named they were orphan receptors with no known ligand. Thus, their nomenclature is rather unique as the common prefix Gpr does not necessarily reflect a structural similarity within the GPCR superfamily, but rather a common lack of available information. Once a Gpr has been deorphanized (or ‘adopted’), they are often renamed to reflect their known ligand (although many groups may continue to refer to them by the Gpr prefix). One can easily imagine that, for very practical reasons, the ‘orphaned’ status of these receptors is easily perpetuated, as orphan receptors are not often selected as the focus of a study, or as the best candidate for follow-up after a screen. Despite this, however, if one assays for expression in an unbiased fashion, many Gprs are highly expressed (Snead and Insel, 2012, Rajkumar et al., 2014), and exciting and novel roles for specific members of the Gpr family have begun to emerge in recent years.

The focus of this review is a summary of what is currently known regarding the functional role of the Gpr family members in the kidney. The kidney plays a key and pivotal role in the regulation of homeostasis, monitoring the concentration of a wide variety of substances in both the blood and in the forming urine; thus, we have a particular interest in how the kidney may utilize novel chemoreceptors in order to maintain homeostasis. In addition, many GPCRs are excellent drug targets (Insel et al., 2015, Overington et al., 2006, Rask-Andersen et al., 2014, Lundstrom, 2009), further increasing the promise of the understudied Gpr family. Here, we will review what is known in the literature regarding renal Gpr receptors, primarily highlighting receptors which have now been deorphanized (adopted) and for which some function has been assigned (Fig. 1; Table 1). We hope that this review will summarize the current state of the field, while also highlighting the promise of this unique and understudied area.

Gpr30 (Adopted name: GPER)

Gpr30, which is also known as G-protein coupled estrogen receptor 1, or GPER, was initially deorphanized by two groups in 2005 as an estrogen receptor (Revankar et al., 2005, Thomas et al., 2005). Gpr30 has been reported to couple to a number of signaling pathways including Ca^{2+} , adenylyl cyclase, transactivation of epidermal growth factor receptors (EGFRs), phosphoinositide 3-kinase (PI3K) and mitogen-activated protein kinases (MAPK) (Prossnitz et al., 2007, Wei et al., 2014, Luo et al., 2012, Ge et al., 2012). In studies beginning in ~2011, evidence has suggested that Gpr30/GPER may also be responsive to aldosterone (Gros et al., 2013, Briet and Schiffrin, 2013, Feldman and Gros, 2011, Wendler and Wehling, 2011, Gros et al., 2011, Ren et al., 2014, Orlowski et al., 2016, De Giusti et al.,

2015), although there is not clear agreement on whether aldosterone is truly a ligand for Gpr30 (summarized in (Barton, 2012), also, see discussion of (Cheng et al., 2014) below). What is clear, however, is that Gpr30 signaling intersects with renal physiology (Gros et al., 2011, Batenburg et al., 2012).

Gpr30 has been reported to localize to a number of segments in the mouse kidney by immunohistochemistry (with antibody fidelity being confirmed by competing signal with the immunogenic peptide)(Cheng et al., 2014). According to the Cheng, et al., study, Gpr30 is expressed primarily in the DCT (distal convoluted tubule) and loop of Henle, with lower expression in the proximal tubule and absent expression in the collecting ducts. This same study also showed that both the level of expression (western blot) and the subcellular localization of Gpr30 is modified by the estrus cycle. Finally, this study additionally used plasma membrane fractions from both whole kidney and from cells overexpressing Gpr30 to assay [³H] ligand binding (of estrogen and aldosterone). Taking advantage of the fact that Gpr30 localizes to the plasma membrane whereas the canonical aldosterone receptor, the mineralocorticoid receptor (MR), is intracellular, they found that plasma membrane fractions bound to estrogen, while the cytosolic fraction (but not the plasma membrane fraction) bound to aldosterone. Thus, they side with the view that GPER does not function as a membrane aldosterone receptor.

With regards to functional roles for Gpr30 in renal physiology, although estrogen has been found to be renoprotective after ischemia-perfusion, it appears that this effect is not dependent upon Gpr30 (Hutchens et al., 2014) – curiously, the same study noted that Gpr30 knockout (KO) animals tend to have reduced plasma creatinine, a topic which certainly deserves further inquiry. A separate study, which used a GPER agonist and GPER knockdown rather than transgenic animals, implied that Gpr30 *does* mediate beneficial effects of estrogen in cultured mesangial cells (by influencing TGF- β 1 signaling)(Li et al., 2014). Finally, in another study, it was demonstrated (Hofmeister et al., 2012) that Gpr30 is necessary for estrogen effects in renal intercalated cells. The authors demonstrated that Gpr30 mRNA is present in distal nephron segments, and showed that estrogen increases [Ca²⁺]_i in wild-type but not Gpr30 KO tubules. It is worth noting, however, that the immunohistochemistry studies in (Cheng et al., 2014) did not report intercalated cell staining.

Gpr41 and 43 (Adopted name: Ffar3 and Ffar2)

Gpr41 and Gpr43 are relatively well-studied Gpr's, although little is known about their roles in the kidney. In 2003, two different groups reported that these two GPCRs are receptors for short chain fatty acids (SCFAs) (Brown et al., 2003, Le et al., 2003), and thus they were renamed free fatty acid receptor 3 (Ffar3, Gpr41) and free fatty acid receptor 2 (Ffar2, Gpr43). Both Gpr41 and Gpr43 couple to G_i (Brown et al., 2003, Le et al., 2003), although Gpr43 has additionally been reported to couple to G_q (Brown et al., 2003, Le et al., 2003). Much of the interest in these two Gpr's was driven by the fact that their ligand, SCFAs, are a byproduct of gut microbial metabolism (Bugaut, 1987). In fact, although SCFAs are found in the μ M range in the plasma, they are virtually undetectable in the plasma of germ free mice (mice without any microbiota) (Perry et al., 2016). Thus, there has been great interest in

Gpr41 and Gpr43 as mediators of microbe-host communication, with studies showing that microbial SCFAs interact with these receptors to mediate various aspects of host physiology, notably adiposity/metabolism (Samuel et al., 2008 2008) and inflammation/immune responses (Maslowski et al., 2009).

With regards to renal function, both Gpr41 (Rajkumar et al., 2014) and Gpr43 are known to be expressed in the kidney (both are in the renal artery (Pluznick et al., 2013) by RT-PCR; other renal localization not yet examined). These receptors are also present in extrarenal blood vessels (Pluznick et al., 2013), and SCFAs delivered intravenously produce an acute hypotensive effect in mice. This hypotensive response to SCFAs is blunted in Gpr41 KO animals, indicating that Gpr41 mediates the bulk of this hypotensive response (Pluznick, et al 2013). In future studies, it will be important to more precisely localize Gpr41 and Gpr43 within the kidney, and to better outline the functional roles of each of these receptors.

Gpr48 (Adopted name: Lgr4)

Gpr48 (also known as LGR4) is part of the type B leucine-rich repeat containing GPCRs (LGRs), with 17 leucine rich repeats in its extracellular domain (Loh et al., 2001). Gpr48 is expressed in several human and mice tissues such as the kidneys, reproductive system, eye, colon, bladder, and pancreas, as well as in certain tumors (Loh et al., 2001, Stykarsdottir et al., 2013, Yi et al., 2013). Gpr48 knockdown causes reduced viability and severe defects in several organs in mice, indicating that GPR48 plays an intricate role during development. In 2011, three different groups showed that the secreted R-Spondin proteins, which are agonists of Wnt/ β -Catenin signaling, are strong ligands for Gpr48 and also for a closely related receptor LGR5 (Glinka et al., 2011, de et al., 2011, Carmon et al., 2011).

In the kidneys, Gpr48 is expressed highly in the cortex with localization seen primarily in the proximal tubules and moderate expression in some distal convoluted tubules but none in the glomeruli (Van et al., 2005, Yi et al., 2013). Several groups have generated whole animal Gpr48 KO mice with distinct gene-targeting strategies to investigate its role in the kidney. In 2006, Kato et al., reported that Gpr48 KO mice were born at a significantly reduced rate than expected mendelian frequencies (Kato et al., 2006). They also noticed that Gpr48 null pups showed a notable decrease in the number and density of glomeruli at P0 and survived only until P2, exhibiting renal hypoplasia, premature uretic bud differentiation and increased plasma creatinine levels. In this paper, the authors noted that the Gpr48 null pups failed to nurse (Kato et al., 2006), which is a known cause of neonatal death. Failure to nurse may be due to their defective functional role of Gpr48 in the olfactory epithelium and vomeronasal organ, (Van et al., 2005) as nursing in mice is strongly mediated by olfaction (Belluscio et al., 1998, Wong et al., 2000). As the mice on this study were still on a mixed background, the same group subsequently followed this work by backcrossing the Gpr48 KO mice at least 10 times onto C57BL/6J, and noticed that the Gpr48 null mice exhibited an even more severe phenotype, with renal hypoplasia and cysts observed as early as E16.5 (Mohri et al., 2011). In agreement with this, other groups have also shown that Gpr48 KO mice exhibit an increased rate of apoptosis in their kidneys, with a reduced expression level of anti-apoptotic factor PAX2 (Mohri et al., 2012). This increase in apoptosis has been hypothesized to cause the observed renal hypoplasia in these Gpr48 KO animals.

In 2014, another Gpr48 KO model was generated and its role in renal development and the cause for cysts in their kidneys were investigated (Dang et al., 2014). In agreement with previous studies, these authors also noted significant perinatal death (~60% of pups died between P0-P1) in Gpr48 KO mice but they found that through breeding and crossbreeding they could reduce embryonic or neonatal lethality. The average kidney size of the Gpr48 KO mice was drastically smaller compared to that of the age matched WT littermates. In addition severe polycystic lesions were observed in ~70% of Gpr48 KO mice (that are past 5 weeks old), along with upregulation of severe fibrotic markers such as connective tissue growth factor (CTGF), fibronectin (FN), and alpha-smooth muscle actin (α -SMA) in both the mRNA and protein level. Normally, with such a high polycystic burden the KW/BW ratio is higher than controls, but in the case of Gpr48 KO animals the KW/BW ratio is still lower than control mice. This intriguing finding can be attributed to the severe renal hypoplasia observed in the Gpr48 KO animals. Furthermore, the authors found that the expression level of both PKD1 and PKD2, genes responsible in formation of polycystic kidney disease (PKD) (Harris, 1999), was significantly weaker in Gpr48 KO animals compared to controls. Simultaneously, they also noticed that signaling molecules involved in the β -catenin/Wnt pathway (also implicated in PKD) (Lal et al., 2008) were upregulated in Gpr48 KO mice. Together, these results strongly implicate Gpr48 in playing an important role in renal development, and demonstrate that deletion of Gpr48 results in severely undersized multicystic kidneys through altered expression levels of PDK1/PDK2 and the β -catenin/Wnt pathway.

Gpr4

In 2003 Ludwig et al., elegantly demonstrated that two orphan GPCRs, Gpr4 and GPR68 (OGR1), respond to changes in extracellular pH (Ludwig et al., 2003) and are not activated by lipids, such as LPC or SPC, as has been previously postulated (Zhu et al., 2001). This revealed for the first time that protons can serve as ligands for GPCRs, and showed (through site-directed mutagenesis) that histidines at key extracellular sites are critical for sensing pH in these GPCRs (Ludwig et al., 2003). We now know that two other GPCRs, GPR65 (TDAG) and GPR132 (G2A), also belong to this unique family of pH sensing GPCRs (Ishii et al., 2005, Murakami et al., 2004). Although these four GPCRs are expressed in various tissues, GPR4 is the only one among this group of pH sensing GPRs that is highly present in the kidney (Sun et al., 2010).

In the kidneys, GPR4 mRNA is detected primarily in the collecting ducts and has been shown to elevate cAMP levels in OMCD cells *in vitro* in response to acidic pH stimuli (Sun et al., 2010). The role of GPR4 in the kidney was further elucidated when it was noted that GPR4 KO mice exhibit impaired net acid excretion (NAE) in the urine, resulting in disruption of systemic acid-base homeostasis. When the blood-gas parameters were analyzed in nonanesthetized mice, GPR4 KOs exhibited nongap metabolic acidosis with lower bicarbonate and CO₂ levels compared to WT mice. Despite metabolic acidosis, GPR4 KO mice had increased urinary pH. This phenotype agrees well with the GPR4 localization in the collecting duct, since it is a major site for acid-base regulation in the kidneys. Furthermore, the cell type composition of intercalated cells (ICs) in the collecting ducts were also found to be altered in the GPR4 KO mice, with an increased number of A-ICs and

reduced number of B-ICs and non-A-non-B cells in GPR4 KO mice compared to WT (Sun et al., 2015).

Surprisingly, GPR4 deletion in mice increases the expression level of calcium sensing receptor (CASR) by two fold in the kidney, both at baseline and also during acidic challenge. This intriguing finding strengthens the potential involvement of CASR in renal acid-base regulation and tightens the link between systemic calcium and pH homeostasis (Sun et al., 2015). In addition, GPR4 expression is also seen in vascular endothelial and smooth muscle cells, brain, lungs, heart and liver (An et al., 1995, Kim et al., 2005, Lum et al., 2003, Mahadevan et al., 1995), where its functional role is not yet completely understood.

Gpr91 (Adopted name: Sucnr1)

In 2004, He et al., reported that the orphan receptor GPR91 is activated by extracts from pig kidneys (He et al., 2004). By performing mass spectrophotometric analysis of the extract, they found that the natural ligand for GPR91 is succinic acid. Succinate is an intermediate of TCA cycle, and thus this study showed that metabolites of major cellular pathways can serve as ligands for orphan GPRs, and highlights the potential for GPRs and related metabolites to be involved in regulation of critical physiological functions beyond their traditional roles. This same study, also showed that the closely related Gpr99 receptor responds to another TCA cycle intermediate alpha-ketoglutarate (Gpr99 will be discussed in detail in the next section).

The basal plasma level of succinate is 1–20 μ M, but it has been shown to increase locally when a tissue's supply and demand for energy is not met, commonly encountered during conditions such as hypoxia, oxidative stress, ischemia, hypertension and diabetes (Sadagopan et al., 2007, Hebert, 2004, Koivunen et al., 2007). In such instances, succinate from the mitochondria is released into the systemic circulation, which elevates plasma succinate levels in the range of the EC₅₀ value of GPR91 (30–60 μ M) (Toma et al., 2008). In addition to high expression in the kidneys, Gpr91 is additionally seen in the liver, blood vessels, white adipose, and in a variety of other tissues (Regard et al., 2008, Rubic et al., 2008, Hakak et al., 2009, Hamel et al., 2014, Correa et al., 2007, Sapieha et al., 2008) where it has been thought to sense succinate, serve as an indicator of mitochondrial stress, and activate downstream physiological mechanisms to regulate homeostasis.

In the initial paper, He et al., detected GPR91 mRNA levels in various nephron segments and JGA by RT-PCR and *in situ* hybridization (He et al., 2004). Furthermore, they demonstrated that intravenous administration of succinate induces hypertension in rodents, caused by renin initiated activation of renin-angiotensin system. Subsequently, GPR91 expression has also been localized in two additional cell types: macula densa (MD) and glomerular endothelium (Toma et al., 2008, Robben et al., 2009). In these cell types, GPR91 has been shown to play an intricate role in paracrine cross talk between distinct nephron segments via succinate, which results in renin release by the juxtaglomerular cells (Vargas et al., 2009, Toma et al., 2008). Future studies will no doubt continue to dissect this intrarenal

communication mechanism, as GPR91- succinate- renin release appears to be involved in regulation of fluid, acid-base and blood pressure homeostasis.

Gpr99 (Adopted name: Oxgr1)

Gpr99 was first identified and found to be expressed in the kidney in 2002 (Wittenberger et al., 2002). In 2004, the same paper that deorphanized Gpr91 (Sucnr1) as a succinate receptor also identified Gpr99 as a receptor for α -ketoglutarate (He et al., 2004); intriguingly, both ligands are intermediates in the Citric Acid Cycle (also known as the Krebs's Cycle). It is well established that the proximal tubule handling of α -ketoglutarate is altered by changes in acid-base balance (Fig. 2). Under normal or acidotic conditions, α -ketoglutarate is reabsorbed (primarily in the proximal tubule) (Martin et al., 1989, Ferrier et al., 1985). However, under alkalotic conditions, net renal reabsorption is converted to net renal secretion as well as net production (Martin et al., 1989, Ferrier et al., 1985, Cheema-Dhadli et al., 2002). Building on this finding, a study in 2013 (Tokonami et al., 2013) showed that these changes in α -ketoglutarate concentration are sensed by Gpr99, which is expressed in the intercalated cells later on in the connecting tubule and connecting duct (Tokonami et al., 2013, Diehl et al., 2016). Thus, α -ketoglutarate signaling to its receptor later on in the nephron serves as an intrarenal and intratubule paracrine signaling mechanism (Tokonami et al., 2013, Peti-Peterdi, 2013, Allison, 2013, Morla et al., 2016). Intercalated cells are critical in the control of acid/base balance, and thus α -ketoglutarate signaling to Gpr99 in the intercalated cells is a mechanism to instruct the intercalated cells to activate pendrin and regulate HCO_3^- to combat the alkalosis. Indeed, mice null for Gpr99 have an impaired ability to respond to an alkali load (Tokonami et al., 2013). This study also demonstrated that α -ketoglutarate stimulates NaCl reabsorption via Gpr99 in intercalated cells (Tokonami et al., 2013), and likely also increases NaCl reabsorption in principal cells (in an Gpr99-independent manner). Gpr99 is thought to signal via G_q (He et al., 2004).

In 2015, an elegant study further expanded on this finding by studying SPAK KO mice; SPAK is a kinase which has been shown to regulate the activity of the sodium chloride cotransporter (NCC) in the distal convoluted tubule (McCormick et al., 2011, Richardson et al., 2008, Chiga et al., 2008). In the absence of SPAK, NCC cannot be activated; thus, these mice can serve as a model to understand compensatory processes which occur with chronic treatment using thiazide diuretics (a commonly prescribed class of anti-hypertensive which inhibits NCC). SPAK KO mice exhibited an integrated compensatory mechanism involving both Gpr99 and α -ketoglutarate (Grimm et al., 2015): an increase in α -ketoglutarate synthesis occurred in the proximal tubule, and a coordinate upregulation of Gpr99 occurred in the intercalated cells. Thus, a paracrine intranephron mechanism was activated which facilitates delivery of α -ketoglutarate to activate Gpr99 and stimulate NaCl reabsorption. This mechanism, then, offers a potential and intriguing insight into mechanisms which may ultimately limit the effectiveness of thiazide diuretics.

APJ – (Adopted name: APLNR)

The apelin receptor (APJ) was first identified by O'Dowd, et al., in 1993 as an orphan GPCR (O'Dowd et al., 1993). APJ closely resembled the angiotensin receptor AT1, with a 54%

identity in the transmembrane regions, but APJ did not respond to angiotensin II. Five years later APJ was deorphanized, when Tatemoto, et al., showed that it responded to a 36- amino acid peptide from bovine stomach extract, which they named apelin (Tatemoto et al., 1998). We now know that both apelin and APJ are detected in various tissues such as the CNS, heart, lungs and kidneys (O'Carroll et al., 2000, Kleinz and Davenport, 2004, Lee et al., 2000, Kleinz et al., 2005, Medhurst et al., 2003, Hus-Citharel et al., 2008) where their role has been elucidated in several physiological and pathophysiological conditions involving regulation of immune functions, fluid homeostasis, bone physiology and embryonic development of the cardiovascular system (Kleinz and Davenport, 2005). In the kidneys, RT-PCR experiments detect APJ mRNA at very high levels in the glomerulus with relatively moderate amounts in the proximal tubules to collecting ducts. In situ hybridization studies in rat kidneys also localized APJ receptor in the glomeruli, with additional labeling seen in the cells along the vasa recta in the inner stripe of outer medulla, and in the vascular wall of glomerular arterioles in both endothelial and vascular smooth muscle cells (Hus-Citharel et al., 2008, O'Carroll et al., 2000).

The role of APJ in mechanisms involving renal fluid homeostasis was evident in APJ KO mice (Roberts et al., 2009). APJ KO mice have a significant defect in concentrating urine during water deprivation, as the urine output volume is not reduced like in that of WT mice. Normally, during conditions of water deprivation, plasma levels of vasopressin (AVP, also known as anti-diuretic hormone) increase and act on the V2 receptors in the kidneys. This results in antidiuresis due to increased levels of apical aquaporin channels in the collecting duct, resulting in reduced urine volume with increased osmolality. APJ KO mice show significant defects in concentrating urine during water deprivation, as the urinary volume is not reduced as it is in WT mice. The urine osmolality is also reduced in APJ KOs compared to WT mice. However, the plasma AVP levels were comparably increased during water deprivation in both WT and APJ KO mice, indicating that the neurosecretion of AVP to osmotic stress is still intact. However, during peripheral administration of dDAVP (a V2 receptor agonist), APJ KO mice showed a significantly attenuated increase in urine osmolality compared to WT mice, suggesting that the renal V2 receptor mediated response to circulating AVP levels is defective. In addition, in APJ KO mice the AVP mRNA levels were elevated in the PVN during basal conditions, and this level did not increase further during dehydration as observed in WTs. Together, it appears that APJ is necessary for a proper response to changes in AVP in the kidneys and regulating systemic fluid homeostasis.

In addition to their role in fluid homeostasis regulation, apelin and APJ has been implicated in renal fibrosis, renal ischemia/reperfusion (I/R) injury and diabetic nephropathy. In the UUO- induced renal fibrosis mice model, both apelin and APJ mRNA levels are upregulated in the kidney, and this contributes to alleviating fibrosis by increasing the NO production in the endothelium through the Akt/eNOS pathway (Tatemoto et al., 2001). Furthermore, recent studies have reported that the apelin – APJ system serves a renoprotective role in I/R injury and diabetic nephropathy. Apelin administration prior to the I/R surgery decreases plasma urea and creatinine levels and increases GFR in the rat model (Sagiroglu et al., 2012). Also, apelin treatment has been shown to upregulate the levels of the antioxidant enzyme, catalase, in the kidneys. This improves recovery from renal and glomerular

hypertrophy in the Ove26 diabetic mice model, independent of any action from the renin-angiotensin system (Day et al., 2013).

Conclusions and Future Directions

Although we have focused here on receptors with known ligands and functions (Fig. 1; Table 1), these few examples only serve to highlight how much is still to be learned in this area: indeed, there are many Gpr's which are known to be expressed in the kidney, but whose ligands and/or functions remain unstudied. Several large-scale screens (Vassilatis et al., 2003, Regard et al., 2008) for tissue expression of GPCRs have identified a number of GPCRs which are expressed in the kidney – in many cases, the functional role (and often the ligands) are unknown. We recently used a Taqman GPCR screen to perform a targeted study for Gpr's in the kidney – as a result, we identified 76 renal Gpr's (Rajkumar et al., 2014). We were impressed to note that the most highly expressed Gpr's were expressed at levels comparable to classic renal receptors including the Angiotensin II receptor and the Arginine Vasopressin Receptor (Rajkumar et al., 2014), implying that renal Gpr's may play important roles in renal physiology, and likely mediate a myriad of functions that are yet to be discovered. This is especially relevant in light of the fact that GPCRs are generally a very druggable class: GPCRs are poised on the plasma membrane to respond to drugs in a cell type-specific manner, making them particularly enticing targets for therapeutics. In fact, it has been estimated that GPCRs represent ~20–60% of current drug targets (Overington et al., 2006, Rask-Andersen et al., 2014, Lundstrom, 2009). As GPRs are classically understudied, it is our hope that uncovering the function of these unsung receptors can lead not only to a heightened understanding of renal physiology, but perhaps future treatments for renal disease.

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Reference List

- Allison SJ. Acid-base disorders: paracrine regulation of acid-base balance. *Nat Rev Nephrol.* 2013; 9:493.
- An S, Tsai C, Goetzl EJ. Cloning, sequencing and tissue distribution of two related G protein-coupled receptor candidates expressed prominently in human lung tissue. *FEBS Lett.* 1995; 375:121–4. [PubMed: 7498459]
- Barton M. Position paper: The membrane estrogen receptor GPER--Clues and questions. *Steroids.* 2012; 77:935–942. [PubMed: 22521564]
- Belluscio L, Gold GH, Nemes A, Axel R. Mice deficient in G(olf) are anosmic. *Neuron.* 1998; 20:69–81. [PubMed: 9459443]
- Briet M, Schiffrin EL. Vascular actions of aldosterone. *J Vasc Res.* 2013; 50:89–99. [PubMed: 23172373]
- Brown AJ, Goldsworthy SM, Barnes AA, Eilert MM, Tcheang L, Daniels D, Muir AI, Wigglesworth MJ, Kinghorn I, Fraser NJ, Pike NB, Strum JC, Stepkowski KM, Murdock PR, Holder JC, Marshall FH, 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]

- Bryksin AV, Matsumura I. Overlap extension PCR cloning: a simple and reliable way to create recombinant plasmids. *Biotechniques*. 2010; 48:463–465. [PubMed: 20569222]
- 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]
- Busse D, Kudella P, Gruning NM, Gisselmann G, Stander S, Luger T, Jacobsen F, Steinstrasser L, Paus R, Gkogkolou P, Bohm M, Hatt H, Benecke H. A Synthetic Sandalwood Odorant Induces Wound-Healing Processes in Human Keratinocytes via the Olfactory Receptor OR2AT4. *J Invest Dermatol*. 2014
- Carmon KS, Gong X, Lin Q, Thomas A, Liu Q. R-spondins function as ligands of the orphan receptors LGR4 and LGR5 to regulate Wnt/beta-catenin signaling. *Proc Natl Acad Sci U S A*. 2011; 108:11452–11457. [PubMed: 21693646]
- Cheema-Dhadli S, Lin SH, Halperin ML. Mechanisms used to dispose of progressively increasing alkali load in rats. *Am J Physiol Renal Physiol*. 2002; 282:F1049–55. [PubMed: 11997321]
- Cheng SB, Dong J, Pang Y, LaRocca J, Hixon M, Thomas P, Filardo EJ. Anatomical location and redistribution of G protein-coupled estrogen receptor-1 during the estrus cycle in mouse kidney and specific binding to estrogens but not aldosterone. *Mol Cell Endocrinol*. 2014; 382:950–9. [PubMed: 24239983]
- Chiga M, Rai T, Yang SS, Ohta A, Takizawa T, Sasaki S, Uchida S. Dietary salt regulates the phosphorylation of OSR1/SPAK kinases and the sodium chloride cotransporter through aldosterone. *Kidney Int*. 2008; 74:1403–9. [PubMed: 18800028]
- Correa PR, Kruglov EA, Thompson M, Leite MF, Dranoff JA, Nathanson MH. Succinate is a paracrine signal for liver damage. *J Hepatol*. 2007; 47:262–9. [PubMed: 17451837]
- Dang Y, Liu B, Xu P, Zhu P, Zhai Y, Liu M, Ye X. Gpr48 deficiency induces polycystic kidney lesions and renal fibrosis in mice by activating wnt signal pathway. *PLoS One*. 2014; 9:e89835. [PubMed: 24595031]
- Day RT, Cavaglieri RC, Feliars D. Apelin retards the progression of diabetic nephropathy. *Am J Physiol Renal Physiol*. 2013; 304:F788–800. [PubMed: 23303408]
- De Giusti VC, Orlowski A, Ciancio MC, Espejo MS, Gonano LA, Caldiz CI, Vila Petroff MG, Villa-Abrille MC, Aiello EA. Aldosterone stimulates the cardiac sodium/bicarbonate cotransporter via activation of the g protein-coupled receptor gpr30. *J Mol Cell Cardiol*. 2015; 89:260–7. [PubMed: 26497404]
- de LW, Barker N, Low TY, Koo BK, Li VS, Teunissen H, Kujala P, Haegebarth A, Peters PJ, van de Wetering M, Stange DE, van Es JE, Guardavaccaro D, Schasfoort RB, Mohri Y, Nishimori K, et al. Lgr5 homologues associate with Wnt receptors and mediate R-spondin signalling. *Nature*. 2011; 476:293–297. [PubMed: 21727895]
- Diehl J, Gries B, Pfeil U, Goldenberg A, Mermer P, Kummer W, Paddenberg R. Expression and localization of GPR91 and GPR99 in murine organs. *Cell Tissue Res*. 2016; 364:245–62. [PubMed: 26590824]
- Dyer J, Salmon KS, Zibrik L, Shirazi-Beechey SP. Expression of sweet taste receptors of the T1R family in the intestinal tract and enteroendocrine cells. *Biochem Soc Trans*. 2005; 33:302–305. [PubMed: 15667333]
- 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]
- Feldmesser E, Olender T, Khen M, Yanai I, Ophir R, Lancet D. Widespread ectopic expression of olfactory receptor genes. *BMC Genomics*. 2006; 7:121. [PubMed: 16716209]
- Ferrier B, Martin M, Baverel G. Reabsorption and secretion of alpha-ketoglutarate along the rat nephron: a micropuncture study. *Am J Physiol*. 1985; 248:F404–12. [PubMed: 3976899]
- Ge C, Yu M, Zhang C. G protein-coupled receptor 30 mediates estrogen-induced proliferation of primordial germ cells via EGFR/Akt/beta-catenin signaling pathway. *Endocrinology*. 2012; 153:3504–16. [PubMed: 22635679]
- Glinka A, Dolde C, Kirsch N, Huang YL, Kazanskaya O, Ingelfinger D, Boutros M, Cruciat CM, Niehrs C. LGR4 and LGR5 are R-spondin receptors mediating Wnt/beta-catenin and Wnt/PCP signalling. *EMBO Rep*. 2011; 12:1055–1061. [PubMed: 21909076]

- Griffin CA, Kafadar KA, Pavlath GK. MOR23 promotes muscle regeneration and regulates cell adhesion and migration. *Dev Cell*. 2009; 17:649–661. [PubMed: 19922870]
- Grimm PR, Lazo-Fernandez Y, Delpire E, Wall SM, Dorsey SG, Weinman EJ, Coleman R, Wade JB, Welling PA. Integrated compensatory network is activated in the absence of NCC phosphorylation. *J Clin Invest*. 2015; 125:2136–50. [PubMed: 25893600]
- Gros R, Ding Q, Sklar LA, Prossnitz EE, Arterburn JB, Chorazyczewski J, Feldman RD. GPR30 expression is required for the mineralocorticoid receptor-independent rapid vascular effects of aldosterone. *Hypertension*. 2011; 57:442–451. [PubMed: 21242460]
- Gros R, Ding QM, Liu BN, Chorazyczewski J, Feldman RD. Aldosterone mediates its rapid effects in vascular endothelial cells through GPER activation. *American Journal of Physiology-Cell Physiology*. 2013; 304:C532–C540. [PubMed: 23283935]
- Hakak Y, Lehmann-Bruinsma K, Phillips S, Le T, Liaw C, Connolly DT, Behan DP. The role of the GPR91 ligand succinate in hematopoiesis. *J Leukoc Biol*. 2009; 85:837–43. [PubMed: 19204147]
- Hamel D, Sanchez M, Duhamel F, Roy O, Honore JC, Noueihed B, Zhou T, Nadeau-Vallee M, Hou X, Lavoie JC, Mitchell G, Mamer OA, Chemtob S. G-protein-coupled receptor 91 and succinate are key contributors in neonatal postcerebral hypoxia-ischemia recovery. *Arterioscler Thromb Vasc Biol*. 2014; 34:285–93. [PubMed: 24285580]
- Harris PC. Autosomal dominant polycystic kidney disease: clues to pathogenesis. *Hum Mol Genet*. 1999; 8:1861–6. [PubMed: 10469838]
- He W, Miao FJ, Lin DC, Schwandner RT, Wang Z, Gao J, Chen JL, Tian H, Ling L. Citric acid cycle intermediates as ligands for orphan G-protein-coupled receptors. *Nature*. 2004; 429:188–93. [PubMed: 15141213]
- Hebert SC. Physiology: orphan detectors of metabolism. *Nature*. 2004; 429:143–5. [PubMed: 15141197]
- Hofmeister MV, Damkier HH, Christensen BM, Olde B, Fredrik Leeb-Lundberg LM, Fenton RA, Praetorius HA, Praetorius J. 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. [PubMed: 21993891]
- Huang AL, Chen X, Hoon MA, Chandrashekar J, Guo W, Trankner D, Ryba NJ, Zuker CS. The cells and logic for mammalian sour taste detection. *Nature*. 2006; 442:934–8. [PubMed: 16929298]
- Hus-Citharel A, Bouby N, Frugiere A, Bodineau L, Gasc JM, Llorens-Cortes C. Effect of apelin on glomerular hemodynamic function in the rat kidney. *Kidney Int*. 2008; 74:486–94. [PubMed: 18509323]
- Hutchens MP, Kosaka Y, Zhang W, Fujiyoshi T, Murphy S, Alkayed N, Anderson S. Estrogen-mediated renoprotection following cardiac arrest and cardiopulmonary resuscitation is robust to GPR30 gene deletion. *PLoS One*. 2014; 9:e99910. [PubMed: 24923556]
- Insel PA, Wilderman A, Zambon AC, Snead AN, Murray F, Aroonsakool N, McDonald DS, Zhou S, McCann T, Zhang L, Sriram K, Chinn AM, Michkov AV, Lynch RM, Overland AC, Corriden R. G Protein-Coupled Receptor (GPCR) Expression in Native Cells: “Novel” endoGPCRs as Physiologic Regulators and Therapeutic Targets. *Mol Pharmacol*. 2015; 88:181–7. [PubMed: 25737495]
- Ishii S, Kihara Y, Shimizu T. Identification of T cell death-associated gene 8 (TDAG8) as a novel acid sensing G-protein-coupled receptor. *J Biol Chem*. 2005; 280:9083–7. [PubMed: 15618224]
- Kang N, Bahk YY, Lee N, Jae Y, Cho YH, Ku CR, Byun Y, Lee EJ, Kim MS, Koo J. Olfactory receptor Olfr544 responding to azelaic acid regulates glucagon secretion in alpha-cells of mouse pancreatic islets. *Biochem Biophys Res Commun*. 2015; 460:616–21. [PubMed: 25804639]
- Kang N, Koo J. Olfactory receptors in non-chemosensory tissues. *BMB Rep*. 2012; 45:612–22. [PubMed: 23186999]
- Kato S, Matsubara M, Matsuo T, Mohri Y, Kazama I, Hatano R, Umezawa A, Nishimori K. 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]
- Kim KS, Ren J, Jiang Y, Ebrahim Q, Tipps R, Cristina K, Xiao YJ, Qiao J, Taylor KL, Lum H, Anand-Apte B, Xu Y. GPR4 plays a critical role in endothelial cell function and mediates the effects of sphingosylphosphorylcholine. *FASEB J*. 2005; 19:819–21. [PubMed: 15857892]

- Kim SH, Yoon YC, Lee AS, Kang N, Koo J, Rhyu MR, Park JH. Expression of human olfactory receptor 10J5 in heart aorta, coronary artery, and endothelial cells and its functional role in angiogenesis. *Biochem Biophys Res Commun*. 2015; 460:404–8. [PubMed: 25791473]
- Kleinz MJ, Davenport AP. Immunocytochemical localization of the endogenous vasoactive peptide apelin to human vascular and endocardial endothelial cells. *Regul Pept*. 2004; 118:119–25. [PubMed: 15003827]
- Kleinz MJ, Davenport AP. Emerging roles of apelin in biology and medicine. *Pharmacol Ther*. 2005; 107:198–211. [PubMed: 15907343]
- Kleinz MJ, Skepper JN, Davenport AP. Immunocytochemical localisation of the apelin receptor, APJ, to human cardiomyocytes, vascular smooth muscle and endothelial cells. *Regul Pept*. 2005; 126:233–40. [PubMed: 15664671]
- Koivunen P, Hirsila M, Remes AM, Hassinen IE, Kivirikko KI, Myllyharju J. Inhibition of hypoxia-inducible factor (HIF) hydroxylases by citric acid cycle intermediates: possible links between cell metabolism and stabilization of HIF. *J Biol Chem*. 2007; 282:4524–32. [PubMed: 17182618]
- Lal M, Song X, Pluznick JL, Di GV, Merrick DM, Rosenblum ND, Chauvet V, Gottardi CJ, Pei Y, Caplan MJ. Polycystin-1 C-terminal tail associates with beta-catenin and inhibits canonical Wnt signaling. *Hum Mol Genet*. 2008; 17:3105–3117. [PubMed: 18632682]
- Le PE, Loison C, Struyf S, Springael JY, Lannoy V, Decobecq ME, Brezillon S, Dupriez V, Vassart G, Van DJ, Parmentier M, Detheux M. 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]
- Lee DK, Cheng R, Nguyen T, Fan T, Kariyawasam AP, Liu Y, Osmond DH, George SR, O'Dowd BF. Characterization of apelin, the ligand for the APJ receptor. *J Neurochem*. 2000; 74:34–41. [PubMed: 10617103]
- Li YC, Ding XS, Li HM, Zhang Y, Bao J. Role of G protein-coupled estrogen receptor 1 in modulating transforming growth factor-beta stimulated mesangial cell extracellular matrix synthesis and migration. *Mol Cell Endocrinol*. 2014; 391:50–9. [PubMed: 24793639]
- 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]
- Ludwig MG, Vanek M, Guerini D, Gasser JA, Jones CE, Junker U, Hofstetter H, Wolf RM, Seuwen K. Proton-sensing G-protein-coupled receptors. *Nature*. 2003; 425:93–8. [PubMed: 12955148]
- Lum H, Qiao J, Walter RJ, Huang F, Subbaiah PV, Kim KS, Holian O. Inflammatory stress increases receptor for lysophosphatidylcholine in human microvascular endothelial cells. *Am J Physiol Heart Circ Physiol*. 2003; 285:H1786–9. [PubMed: 12805023]
- Lundstrom K. An overview on GPCRs and drug discovery: structure-based drug design and structural biology on GPCRs. *Methods Mol Biol*. 2009; 552:51–66. [PubMed: 19513641]
- Luo LJ, Liu F, Lin ZK, Xie YF, Xu JL, Tong QC, Shu R. Genistein regulates the IL-1 beta induced activation of MAPKs in human periodontal ligament cells through G protein-coupled receptor 30. *Arch Biochem Biophys*. 2012; 522:9–16. [PubMed: 22521737]
- Mahadevan MS, Baird S, Bailly JE, Shutler GG, Sabourin LA, Tsilfidis C, Neville CE, Narang M, Korneluk RG. Isolation of a novel G protein-coupled receptor (GPR4) localized to chromosome 19q13.3. *Genomics*. 1995; 30:84–8. [PubMed: 8595909]
- Martin M, Ferrier B, Baverel G. Transport and utilization of alpha-ketoglutarate by the rat kidney in vivo. *Pflugers Arch*. 1989; 413:217–24. [PubMed: 2717372]
- Maslowski KM, Vieira AT, Ng A, Kranich J, Sierro F, Yu D, Schilter HC, Rolph MS, Mackay F, Artis D, Xavier RJ, Teixeira MM, Mackay CR. Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. *Nature*. 2009; 461:1282–1286. [PubMed: 19865172]
- McCormick JA, Mutig K, Nelson JH, Saritas T, Hoorn EJ, Yang CL, Rogers S, Curry J, Delpire E, Bachmann S, Ellison DH. A SPAK isoform switch modulates renal salt transport and blood pressure. *Cell Metab*. 2011; 14:352–64. [PubMed: 21907141]
- Medhurst AD, Jennings CA, Robbins MJ, Davis RP, Ellis C, Winborn KY, Lawrie KW, Hervieu G, Riley G, Bolaky JE, Herrity NC, Murdock P, Darker JG. Pharmacological and

immunohistochemical characterization of the APJ receptor and its endogenous ligand apelin. *J Neurochem.* 2003; 84:1162–72. [PubMed: 12603839]

- Mohri Y, Oyama K, Akamatsu A, Kato S, Nishimori K. 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]
- Mohri Y, Oyama K, Sone M, Akamatsu A, Nishimori K. 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]
- Morla L, Edwards A, Crambert G. New insights into sodium transport regulation in the distal nephron: Role of G-protein coupled receptors. *World J Biol Chem.* 2016; 7:44–63. [PubMed: 26981195]
- Murakami N, Yokomizo T, Okuno T, Shimizu T. G2A is a proton-sensing G-protein-coupled receptor antagonized by lysophosphatidylcholine. *J Biol Chem.* 2004; 279:42484–91. [PubMed: 15280385]
- O'Carroll AM, Selby TL, Palkovits M, Lolait SJ. Distribution of mRNA encoding B78/apj, the rat homologue of the human APJ receptor, and its endogenous ligand apelin in brain and peripheral tissues. *Biochim Biophys Acta.* 2000; 1492:72–80. [PubMed: 11004481]
- O'Dowd BF, Heiber M, Chan A, Heng HH, Tsui LC, Kennedy JL, Shi X, Petronis A, George SR, Nguyen T. A human gene that shows identity with the gene encoding the angiotensin receptor is located on chromosome 11. *Gene.* 1993; 136:355–60. [PubMed: 8294032]
- Orlowski A, De Giusti VC, Ciancio MC, Espejo MS, Aiello EA. The cardiac electrogenic sodium/bicarbonate cotransporter (NBCe1) is activated by aldosterone through the G protein-coupled receptor 30 (GPR 30). *Channels (Austin).* 2016
- Overington JP, Al-Lazikani B, Hopkins AL. How many drug targets are there? *Nat Rev Drug Discov.* 2006; 5:993–6. [PubMed: 17139284]
- Perry RJ, Peng L, Barry NA, Cline GW, Zhang D, Cardone RL, Petersen KF, Kibbey RG, Goodman AL, Shulman GI. Acetate mediates a microbiome-brain-beta-cell axis to promote metabolic syndrome. *Nature.* 2016; 534:213–7. [PubMed: 27279214]
- Peti-Peterdi J. Mitochondrial TCA cycle intermediates regulate body fluid and acid-base balance. *J Clin Invest.* 2013; 123:2788–90. [PubMed: 23926603]
- Pluznick JL. Renal and cardiovascular sensory receptors and blood pressure regulation. *Am J Physiol Renal Physiol.* 2013; 305:F439–F444. [PubMed: 23761671]
- Pluznick JL, Caplan MJ. Novel sensory signaling systems in the kidney. *Curr Opin Nephrol Hypertens.* 2012
- Pluznick JL, Protzko RJ, Gevorgyan H, Peterlin Z, Sipos A, Han J, Brunet I, Wan LX, Rey F, Wang T, Firestein SJ, Yanagisawa M, Gordon JI, Eichmann A, Peti-Peterdi J, Caplan MJ. Olfactory receptor responding to gut microbiota-derived signals plays a role in renin secretion and blood pressure regulation. *Proc Natl Acad Sci U S A.* 2013; 110:4410–4415. [PubMed: 23401498]
- Pluznick JL, Zou DJ, Zhang X, Yan Q, Rodriguez-Gil DJ, Eisner C, Wells E, Greer CA, Wang T, Firestein S, Schnermann J, Caplan MJ. Functional expression of the olfactory signaling system in the kidney. *Proc Natl Acad Sci U S A.* 2009; 106:2059–2064. [PubMed: 19174512]
- Prossnitz ER, Arterburn JB, Sklar LA. GPR30: A G protein-coupled receptor for estrogen. *Mol Cell Endocrinol.* 2007; 265–266:138–42.
- Rajkumar P, Aisenberg WH, Acres OW, Protzko RJ, Pluznick JL. Identification and characterization of novel renal sensory receptors. *PLoS One.* 2014; 9:e111053. [PubMed: 25340336]
- Rask-Andersen M, Masuram S, Schioth HB. The druggable genome: Evaluation of drug targets in clinical trials suggests major shifts in molecular class and indication. *Annu Rev Pharmacol Toxicol.* 2014; 54:9–26. [PubMed: 24016212]
- Regard JB, Sato IT, Coughlin SR. Anatomical profiling of G protein-coupled receptor expression. *Cell.* 2008; 135:561–71. [PubMed: 18984166]
- Ren Y, D'Ambrosio MA, Garvin JL, Leung P, Kutskill K, Wang H, Peterson EL, Carretero OA. Aldosterone sensitizes connecting tubule glomerular feedback via the aldosterone receptor GPR30. *Am J Physiol Renal Physiol.* 2014; 307:F427–34. [PubMed: 24966088]
- Revankar CM, Cimino DF, Sklar LA, Arterburn JB, Prossnitz ER. A transmembrane intracellular estrogen receptor mediates rapid cell signaling. *Science.* 2005; 307:1625–30. [PubMed: 15705806]

- Richardson C, Rafiqi FH, Karlsson HK, Moleleki N, Vandewalle A, Campbell DG, Morrice NA, Alessi DR. Activation of the thiazide-sensitive Na⁺-Cl⁻ cotransporter by the WNK-regulated kinases SPAK and OSR1. *J Cell Sci*. 2008; 121:675–84. [PubMed: 18270262]
- Robben JH, Fenton RA, Vargas SL, Schweer H, Peti-Peterdi J, Deen PM, Milligan G. Localization of the succinate receptor in the distal nephron and its signaling in polarized MDCK cells. *Kidney Int*. 2009; 76:1258–1267. [PubMed: 19776718]
- Roberts EM, Newson MJ, Pope GR, Landgraf R, Lolait SJ, O'Carroll AM. Abnormal fluid homeostasis in apelin receptor knockout mice. *J Endocrinol*. 2009; 202:453–62. [PubMed: 19578099]
- Rubic T, Lametschwandtner G, Jost S, Hinteregger S, Kund J, Carballido-Perrig N, Schwarzler C, Junt T, Voshol H, Meingassner JG, Mao X, Werner G, Rot A, Carballido JM. Triggering the succinate receptor GPR91 on dendritic cells enhances immunity. *Nat Immunol*. 2008; 9:1261–9. [PubMed: 18820681]
- Sadagopan N, Li W, Roberds SL, Major T, Preston GM, Yu Y, Tones MA. Circulating succinate is elevated in rodent models of hypertension and metabolic disease. *Am J Hypertens*. 2007; 20:1209–15. [PubMed: 17954369]
- Sagiroglu T, Torun N, Yagci M, Yalta T, Sagiroglu G, Oguz S. Effects of apelin and leptin on renal functions following renal ischemia/reperfusion: An experimental study. *Exp Ther Med*. 2012; 3:908–914. [PubMed: 22969992]
- Samuel BS, Shaito A, Motoike T, Rey FE, Backhed F, Manchester JK, Hammer RE, Williams SC, Crowley J, Yanagisawa M, Gordon JI. 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 U S A*. 2008; 105:16767–16772. [PubMed: 18931303]
- Sapieha P, Sirinyan M, Hamel D, Zaniolo K, Joyal JS, Cho JH, Honore JC, Kermorvant-Duchemin E, Varma DR, Tremblay S, Leduc M, Rihakova L, Hardy P, Klein WH, Mu X, Mamer O, et al. The succinate receptor GPR91 in neurons has a major role in retinal angiogenesis. *Nat Med*. 2008; 14:1067–76. [PubMed: 18836459]
- Shah AS, Ben-Shahar Y, Moninger TO, Kline JN, Welsh MJ. Motile cilia of human airway epithelia are chemosensory. *Science*. 2009; 325:1131–1134. [PubMed: 19628819]
- 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]
- Spehr M, Gisselmann G, Poplawski A, Riffell JA, Wetzel CH, Zimmer RK, Hatt H. Identification of a testicular odorant receptor mediating human sperm chemotaxis. *Science*. 2003; 299:2054–2058. [PubMed: 12663925]
- Styrkarsdottir U, Thorleifsson G, Sulem P, Gudbjartsson DF, Sigurdsson A, Jonasdottir A, Jonasdottir A, Oddsson A, Helgason A, Magnusson OT, Walters GB, Frigge ML, Helgadóttir HT, Johannsdóttir H, Bergsteinsdóttir K, Ogmundsdóttir MH, et al. Nonsense mutation in the LGR4 gene is associated with several human diseases and other traits. *Nature*. 2013; 497:517–520. [PubMed: 23644456]
- Sun X, Stephens L, DuBose TD Jr, Petrovic S. Adaptation by the collecting duct to an exogenous acid load is blunted by deletion of the proton-sensing receptor GPR4. *Am J Physiol Renal Physiol*. 2015; 309:F120–36. [PubMed: 25972512]
- Sun X, Yang LV, Tiegs BC, Arend LJ, McGraw DW, Penn RB, Petrovic S. Deletion of the pH sensor GPR4 decreases renal acid excretion. *J Am Soc Nephrol*. 2010; 21:1745–55. [PubMed: 20798260]
- Tatemoto K, Hosoya M, Habata Y, Fujii R, Kakegawa T, Zou MX, Kawamata Y, Fukusumi S, Hinuma S, Kitada C, Kurokawa T, Onda H, Fujino M. Isolation and characterization of a novel endogenous peptide ligand for the human APJ receptor. *Biochem Biophys Res Commun*. 1998; 251:471–6. [PubMed: 9792798]
- Tatemoto K, Takayama K, Zou MX, Kumaki I, Zhang W, Kumano K, Fujimiya M. The novel peptide apelin lowers blood pressure via a nitric oxide-dependent mechanism. *Regul Pept*. 2001; 99:87–92. [PubMed: 11384769]
- Thomas P, Pang Y, Filardo EJ, Dong J. Identity of an estrogen membrane receptor coupled to a G protein in human breast cancer cells. *Endocrinology*. 2005; 146:624–32. [PubMed: 15539556]

- Tokonami N, Morla L, Centeno G, Mordasini D, Ramakrishnan SK, Nikolaeva S, Wagner CA, Bonny O, Houillier P, Doucet A, Firsov D. α -Ketoglutarate regulates acid-base balance through an intrarenal paracrine mechanism. *J Clin Invest*. 2013; 123:3166–71. [PubMed: 23934124]
- Toma I, Kang JJ, Sipos A, Vargas S, Bansal E, Hanner F, Meer E, Peti-Peterdi J. 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]
- 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]
- Vargas SL, Toma I, Kang JJ, Meer EJ, Peti-Peterdi J. Activation of the succinate receptor GPR91 in macula densa cells causes renin release. *J Am Soc Nephrol*. 2009; 20:1002–11. [PubMed: 19389848]
- Vassilatis DK, Hohmann JG, Zeng H, Li F, Ranchalis JE, Mortrud MT, Brown A, Rodriguez SS, Weller JR, Wright AC, Bergmann JE, Gaitanaris GA. The G protein-coupled receptor repertoires of human and mouse. *Proc Natl Acad Sci U S A*. 2003; 100:4903–8. [PubMed: 12679517]
- Wei W, Chen ZJ, Zhang KS, Yang XL, Wu YM, Chen XH, Huang HB, Liu HL, Cai SH, Du J, Wang HS. The activation of G protein-coupled receptor 30 (GPR30) inhibits proliferation of estrogen receptor-negative breast cancer cells in vitro and in vivo. *Cell Death Dis*. 2014; 5:e1428. [PubMed: 25275589]
- Wendler A, Wehling M. Is GPR30 the membrane aldosterone receptor postulated 20 years ago? *Hypertension*. 2011; 57:e16. [PubMed: 21422381]
- Wittenberger T, Hellebrand S, Munck A, Kreienkamp HJ, Schaller HC, Hampe W. GPR99, a new G protein-coupled receptor with homology to a new subgroup of nucleotide receptors. *BMC Genomics*. 2002; 3:17. [PubMed: 12098360]
- Wong ST, Trinh K, Hacker B, Chan GC, Lowe G, Gaggari A, Xia Z, Gold GH, Storm DR. Disruption of the type III adenylyl cyclase gene leads to peripheral and behavioral anosmia in transgenic mice. *Neuron*. 2000; 27:487–497. [PubMed: 11055432]
- Wu C, Jia Y, Lee JH, Kim Y, Sekharan S, Batista VS, Lee SJ. Activation of OR1A1 suppresses PPAR- γ expression by inducing HES-1 in cultured hepatocytes. *Int J Biochem Cell Biol*. 2015; 64:75–80. [PubMed: 25817041]
- Yi J, Xiong W, Gong X, Bellister S, Ellis LM, Liu Q. Analysis of LGR4 receptor distribution in human and mouse tissues. *PLoS One*. 2013; 8:e78144. [PubMed: 24205130]
- Young RL, Chia B, Isaacs NJ, Ma J, Khoo J, Wu T, Horowitz M, Rayner CK. Disordered control of intestinal sweet taste receptor expression and glucose absorption in type 2 diabetes. *Diabetes*. 2013; 62:3532–41. [PubMed: 23761104]
- Zhu K, Baudhuin LM, Hong G, Williams FS, Cristina KL, Kabarowski JH, Witte ON, Xu Y. Sphingosylphosphorylcholine and lysophosphatidylcholine are ligands for the G protein-coupled receptor GPR4. *J Biol Chem*. 2001; 276:41325–35. [PubMed: 11535583]

Figure 1. Schematic illustration of the localization of GPRs in the kidney. Nephron segments are labelled and the GPRs that have been shown to be present in each segment are listed.

Figure 2.

Gpr99/Oxgr1 in the intercalated cells of the collecting duct is activated in response to changes in the handling of α -ketoglutarate (α -KG) in the proximal tubule. Under acidotic conditions, the proximal tubule reabsorbs α -KG, thereby largely preventing downstream activation of Gpr99 in intercalated cells. However, under conditions of alkalosis, proximal tubules secrete α -KG, thereby activating downstream Gpr99 in the intercalated cells. Gpr99 activation leads to the activation of transporters that combat the alkalosis. A, apical. B, basolateral.

Table 1

Summary of the G-protein, agonist, nephron localization and function of orphanized GPRs in the kidney

Gpr name	Adopted name	G-protein	Ligand	Renal Localization	Renal-related function
Gpr30	GPER	Gs, Gq	Estrogen	DCT, loop of henle	Renoprotective role
Gpr41	Ffar3	Gi	Short chain fatty acids	Renal artery	Blood pressure regulation (Gpr41)
Gpr43	Ffar2	Gi/Gq	Short chain fatty acids	Renal artery	Unknown
Gpr48	LGR4	Gs	R-spondins	Primarily in the PTs	Renal development
GPR4		G _s	pH/protons	Collecting duct	Acid-base homeostasis
GPR91	Sucnr1	Gq, Gi	Succinate	JGA, macula densa and glomerular epithelium	Blood pressure regulation
GPR99	Oxgr1	Gq	α-ketoglutarate	Intercalated cells	Acid-base homeostasis
API	APLNR	Gi	Apelin	Primarily in glomerulus; moderate levels in PTs to CDs	Fluid homeostasis

DCT (distal convoluted tubule), JGA (juxtaglomerular apparatus), PTs (proximal tubules), DTs (distal tubules), CDs (collecting ducts)