How does your kidney smell? Emerging roles for olfactory receptors in renal function

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Abstract

Olfactory receptors (ORs) are chemosensors that are responsible for one's sense of smell. In addition to this specialized role in the nose, recent evidence suggests that ORs are also found in a variety of additional tissues including the kidney. As this list of renal ORs continues to expand, it is becoming clear that these ORs play important roles in renal and whole-body physiology, including a novel role in blood pressure regulation. In this review, we highlight important considerations that are crucial when studying ORs, and present the current literature on renal ORs and their emerging relevance in maintaining renal function.

Introduction

Olfactory receptors (ORs) are 7 transmembrane domain G protein-coupled chemosensors that mediate the sense of smell in the nose. Localized to the cilia on the tips of olfactory sensory neurons (OSNs), they exhibit exquisite sensitivity to a diverse range of volatile odorants [1]. First identified in 1991 by Linda Buck and Richard Axel, it is now known that there are more than 1000 OR genes in mice and roughly 350 in humans making them the largest gene family in the genome [2–4]. Despite the diversity of molecules that activate these receptors, they all signal through a conserved downstream signaling pathway whereby stimulation by a volatile odorant leads to increased intracellular cAMP which depolarizes the OSN [5–7].

In the seminal paper that first described ORs, an assumption was made that OR expression would be restricted to OSNs given their sensory function [1]. While it is true that the expression level of ORs is highest within the olfactory epithelium (OE), it is now clear that at least some ORs are expressed in a variety of additional tissues. With new techniques such as whole transcriptome sequencing, the list of 'ectopic ORs' has greatly expanded in the last few years, and these sites now include the GI tract, muscle, heart, pancreas, liver, lung and the skin [8–19]. While the physiological functions that these ORs play in non-sensory tissues is an ongoing area of research, it is evident that ORs are serving important roles in

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physiology. Notably, murine and human ORs have been found in sperm and play a key role in sperm chemotaxis [10;16]. In addition, MOR23 is found in muscle myocytes where it regulates migration and adhesion and contributes to muscle regeneration [11]. The functional importance of these ORs clearly indicates that these receptors are likely playing novel roles in a variety of different tissues.

Given its sensory functions, the kidney appears to be an ideal organ to take advantage of OR signaling. The epithelial lining of the kidney comes in contact with a diverse range of chemicals, and it must keep careful track of the composition of the tubular fluid as it moves through the different segments of the nephron. The kidney adjusts its filtration, reabsorption and secretion rates in response to changes in electrolytes and metabolites; thus, it is well-suited to take advantage of specialized chemosensors such as ORs, in order to maintain homeostasis. In this review, we will begin by outlining challenges specific to OR biology which shape these investigations, and subsequently will focus on the identification of individual renal ORs and their roles in renal physiology.

Special considerations and challenges of studying ORs

The 'ectopic' expression of sensory receptors such as ORs is an exciting and emerging field. However, there are a number of experimental challenges that are specific to the study of ORs, and it is imperative that one understands these challenges in order to properly evaluate and understand data regarding OR expression in the kidney and elsewhere. Therefore, we will begin by briefly reviewing OR-specific 'best practices'. First, very few antibodies for ORs are available. While G protein-coupled receptors in general tend not to be particularly antigenic, ORs are persistently difficult to generate antibodies against (despite enormous efforts in this area). Out of the 1000 murine ORs and 350 human ORs, there are only a few antibodies which appear reliable: MOR28 [20–22], M50 [23], M71 [23], MOR256-17 [24], MOR11-4 [22], mOR37A-E [24], I7 [21], mOR-EG [21], MOR10 [25], MOR18-2 [26], MOR256-50 [27] and MOR42-3 [27]. Of these, the only OR expressed in the kidney is MOR18-2, although this antibody strongly cross-reacts with a mitochondrial protein when used outside the OE [26]. It is important to note that although numerous additional OR antibodies are readily available for purchase via multiple vendors and companies, to our knowledge only two commercially available OR antibodies have been successfully validated (MOR256-50 and MOR42-3 [27]) – note that an antibody for MOR127-1 could not be validated in this same reference). We and others have attempted to validate a great number of additional commercial antibodies, to no avail. Therefore, if one wishes to employ an OR antibody which has not been previously published, proper validation is absolutely critical – typically, at a minimum, a demonstration that at least one (preferably both) of the following are true: (a) the antibody gives the expected staining pattern in the OE (if the expression pattern for that particular OR is not known, *in situ* hybridization coupled with immunohistochemistry would be the proper demonstration of specificity), and (b) the antibody recognizes cells transfected with the target protein (as in [26;27]). However, even with this validation, it is worth bearing in mind that a positive result would provide key evidence that the antibody recognizes its intended target, but would not mean that the antibody is *specific* for the intended target - as opposed to the other ~1000 ORs.

In the absence of antibodies, one often turns to other methods, including transgenic mice (i.e., with GFP or LacZ reporters) and RNA expression. ORs have an 'ancient' genomic structure – all mammalian ORs have single-exon coding sequences (although introns can be present in OR genes upstream of the coding exon [28; 29]). Therefore, when using RT-PCR it is important to include mock controls for ORs (where no reverse transcriptase enzyme is added to the RT reaction) as genomic DNA and RNA will yield the same size bands for primers directed against the coding sequence. Likewise, simply because the OR gene family is so large, it is important to sequence RT-PCR products to assure identity – with 1000 murine ORs which all have significant sequence similarity, even the most carefully designed primers may be able to cross-react with a 'sibling' of the intended target. Similarly, *in situ* hybridization is often employed for OR localization, and once again one must take care when designing probes that they are specific for the intended OR. When available, knockout mice can be utilized to confirm specificity of *in situ* or antibody signal. When knockout mice are not available, the number of glomeruli in the olfactory bulb which express the OR is a decent surrogate to gauge specificity of an *in situ* probe or antibody (if the probe is specific for a single OR, one would expect to see signal in 2–4 glomeruli [30]; it is imperative that an *in situ* looking at OR expression in glomeruli be isotopic due to the low level of OR mRNA expression in axons).

The high sequence similarity within this large gene family presents an additional challenge – identifying orthologs across species. When comparing rat and murine ORs, for example, both gene families have ~1000 members, and all of them have similarity to one another. Identifying an ortholog based on sequence similarity alone becomes quite difficult. Once a putative ortholog is identified based on sequence, to prove functional relevance one ought to demonstrate that the ORs are *functional* orthologs (i.e., respond to the same ligand).

Indeed, when studying any G protein-coupled receptor, one typically would consider potential roles for the ligand – however, most ORs are 'orphan' receptors, with no known ligand. This is certainly a challenge for the field. There are several well-developed assays that can be used to screen ORs for potential ligands – for example, calcium signaling in HEK cells [31], cAMP-mediated CFTR activation in oocytes [32], or cAMP-mediated luciferase activation in HEK cells [33]. However, all of these assays absolutely require, as a prerequisite, that the OR be expressed on the plasma membrane. For reasons which remain somewhat unclear, although ORs appear to efficiently traffic to the cell surface *in vivo*, they typically remain trapped in the endoplasmic reticulum when expressed exogenously in cell lines [34–36]. This frustrating fact means that screening an OR for potential ligands in a high throughput *in vitro* fashion is not as straightforward as one would hope. Given this, there are several approaches that one could take: first of all, the clearest solution is to screen ORs which Nature has expressed for us – that is, using native OE to test for potential ligands. Typically, potential ligands are tested while calcium responses are monitored, and if an OSN exhibits a calcium response to a particular ligand, then single-cell RT-PCR will be used to identify the receptor expressed in that OSN [37] (dogma holds that each OSN expresses one, and only one, receptor, in a monoallelic fashion [38]). Although in many ways this approach is the most straightforward, it is technically demanding, is not high-throughput, and without the use of GFP or another marker it is difficult to focus research on

a particular OR. A second possible approach to screening ORs is to use a variety of aids to help the OR achieve surface expression when exogenously expressed *in vitro*. A number of studies have identified either chaperones or N-terminal tags which aid in OR surface expression [39–53], and when successful this allows for a high-throughput approach focused on a specific OR.

Finally, careful and elegant work has found that the expression of ORs exhibits strong developmental regulation in the OE – that is, different ORs may be strategically expressed at different developmental time points [54]. Furthermore, even in an OSN, there is a 4-day lag in the onset of OR expression [55]. Therefore, although it is unknown whether temporal regulation of expression takes place in tissues beyond the OE, it is worth noting that the 'absence' of OR expression does not necessarily mean that the OR is never expressed in that tissue - but rather that it is not expressed at that time point.

Characterizing OR signaling in the kidney

Despite the challenges of studying ORs, significant progress has been made in the characterization of renal ORs. In this section of the review, we will begin by discussing the identification of renal ORs and components of their downstream signaling, and then explore their relevance to both renal and whole body physiology.

AC3 and G_{olf}

Despite the fact that there are more than 1000 ORs (mice), all mammalian ORs - at least in the nose - signal through a conserved downstream signaling pathway. Upon OR-odorant binding, the trimeric olfactory G protein ($G_{olfactory}$ or G_{olf}) is activated, triggering the stimulation of membrane-bound adenylate cyclase 3 (AC3) (Fig. 1A) [5–7]. While this signaling pathway is obligatory for olfaction (mice null for AC3 cannot smell), the components of this pathway are also expressed outside of the nose [13; 56–58], and one of these sites is the kidney. AC3 and G_{olf} are both expressed in the murine kidney at the transcript and protein level [59], and antibodies have localized them to the distal convoluted tubule and to an extremely specialized structure known as the macula densa (MD). The MD is a group of tightly packed sensory cells that are localized at the junction between the thick ascending limb and the distal convoluted tubule, where the nephron loops back to the afferent arteriole feeding its own parent glomerulus. MD cells take advantage of this unique placement to monitor the composition of the tubular fluid in the distal nephron, and then communicate this information back to the afferent arteriole feeding the parent glomerulus. For example, if the MD cells detect a decrease in the NaCl concentration in the filtrate, they will 'tell' the afferent arteriole/glomerulus to increase both glomerular filtration rate (GFR) and renin secretion. Ultimately, both of these actions serve to increase NaCl concentration in the filtrate back toward normal. This fine-tuning of GFR regulation allows for constant and precise regulation at the single nephron level, a process known as tubuloglomerular feedback (TGF).

Consistent with localization to the MD, AC3 knockout mice were found to present with both decreased GFR and decreased plasma renin. Therefore, as AC3 and G_{olf} both localize to the MD and AC3 knockout mice exhibit an altered GFR, it was hypothesized that that the

decreased GFR is due to an altered TGF response. However, when TGF was measured in these mice using stop-flow pressure with artificial tubular fluid, the response was normal. It should be noted that, to date, the individual ORs that are upstream of G_{olf} and AC3 in the MD have not been identified. As ORs often respond to individual metabolites (see below), it is likely that the absence of an altered TGF response in the AC3 KO mice may due to the fact that the artificial perfusate was lacking key OR ligands/metabolites. Nonetheless, it is clear that AC3 and G_{olf} do play important functional roles within the renal nephron.

Olfactory receptors

Given the expression of both AC3 and G_{olf} in the murine kidney, it is reasonable to assume that individual ORs are also found in the kidney. Indeed, using a degenerate primer screening approach that takes advantage of the incredible sequence similarity amongst ORs, 6 ORs were initially found to be expressed in whole murine kidney [59]. Further analysis in kidneys from multiple independent mice determined that 4 of these original 6 ORs are consistently expressed in every sample examined. As such, this initial screen revealed 4 novel renal ORs (Olfr78, Olfr90, Olfr1392 and Olfr1393). As degenerate primer screens are likely to pick out only the most highly expressed ORs, more recent targeted RT-PCR screens have also been performed to identify additional renal ORs [60]. Using this strategy, an additional 6 ORs were identified in whole kidney (Olfr99, Olfr545, Olfr691, Olfr693, Olfr31 and Olfr1426). All 10 of these murine renal ORs have been cloned from the kidney from start to stop confirming full-length expression of the coding mRNA (Table 1). In addition to targeted screens, renal ORs have also been identified in mice by microarray studies. Notably, several ORs were found to be expressed by microarray analysis in isolated Juxtaglomerular cells or in renin-containing cells, and their expression may be developmentally regulated (Table 1) [61]. In the future, it will be important to confirm these microarray data by sequencing and to examine their potential developmental regulation in more detail. There are also a number of intriguing RNA sequencing screens that have found renal OR expression in different segments of the nephron. While this data is currently unpublished, the raw datasets are readily available in the GenitoUrinary Development Molecular Anatomy Project (GUDMAP.org).

Renal OR expression is not unique to the mouse – indeed, ORs are also known to be expressed in the rat and human (Table 1). A recent RNA sequencing study on human tissues found that ORs are broadly expressed in different tissues and at least 13 different ORs are expressed in human kidney (excluding pseudogenes) [62]. Similar findings have emerged in the rat. Using hand-dissected nephron segments and isolated glomeruli, the Knepper lab has localized 5 different ORs within the rat nephron [63]. It is important to keep in mind that identification of functional orthologs based on sequence identity alone is usually not possible. Thus, it will be crucial to determine the localization and ligand profiles of this expanding list of renal ORs in order to determine their common functions. To date, a handful of ORs have been characterized and we will explore what is known about these ORs in the next few sections.

OR localization

The renal nephron is comprised of a number of specialized cell types, all with important and unique functions. Therefore, it is important to know where these renal ORs are expressed in order to understand potential physiological functions. As noted above, antibodies for these receptors are consistently unreliable and very few exist for renal ORs. Therefore, alternative methods are often used to determine OR localization. Using hand-dissected nephron segments and isolated glomeruli, all 5 rat identified renal ORs were localized within the kidney [63]. One of these, OR1104, is highly expressed in a single nephron segment – the distal convoluted tubule – while others are found more widely distributed along the length of the nephron (Table 1). Two ORs are exclusively expressed in the rat glomeruli, although the individual cell types are not yet known. In addition, mouse renal Olfr90 is expressed in an MD cell line [59]. While not yet confirmed *in vivo*, this data suggests that Olfr90 may be one of the ORs that signals via AC3 and G_{olf} and could be participating in the AC3-mediated renin release/GFR response. Finally, using a lacZ reporter from a knockout mouse, Olfr78 localizes to the renal afferent arteriole, as well as large renal vessels (i.e. renal artery), and the physiological function of this OR is expanded on in detail below.

While the majority of renal ORs have not yet been localized, it is likely (based on both published and unpublished data) that they are widely distributed throughout the nephron. However, AC3 and G_{olf} display a much more restricted localization pattern as they are both found primarily in the distal tubule and MD [59]. While AC3 and G_{olf} are thought to be the obligate downstream signaling molecules in OSNs, it does not appear to be the case in the kidney. Since ORs have been found in cell types that lack AC3 and G_{olf} (i.e. Olfr78 in the afferent arteriole [64]), these receptors clearly must be signaling through a different G protein. Consistent with this, ORs *in vitro* can also couple to G_s (or, under specific conditions, G_q) [31; 32; 39; 60; 64; 65]. In addition, a handful of ORs have been found to be expressed in the vomeronasal organ, the site of pheromone sensing in the mouse, where they are also thought to couple to other G proteins [66; 67]. Additionally, it is also possible that the renal ORs would signal through AC3 but not G_{olf}, or vice versa. This is supported by the fact that AC3 can be stimulated by other G_s proteins [6; 58]. Clearly additional studies are required to determine the complete expression pattern of ORs within in the kidney and to delineate their downstream signaling (Fig. 1B).

OR ligands

Most ORs are orphan receptors with no known ligands, and the subset of renal ORs are no exception (Table 1). Deorphanizing these receptors is a critical step in determining the function of these renal ORs, and to date, a few of these renal receptors now have known ligands. As mentioned above, functional heterologous expression must be achieved before ligand screening can occur *in vitro*. To date, with the help of various tags and chaperone proteins, 9 different renal murine ORs have been found to traffic to the cell surface in HEK293T cells [39; 60]. Ligand screens have been performed on these ORs, leading to the identification of several different OR-ligand pairs. Olfr78 and its human ortholog hOR51E2 both respond to short chain fatty acids (SCFAs) and the functional relevance of this is discussed in detail below. Olfr691 responds to a wide range of short and medium chain fatty acids [60; 68] (Table 1). Notably, one of these ligands, valproate, has been used as an

antiepileptic drug and patients have been shown to develop Fanconi syndrome [69; 70]. This link could potentially reveal a novel mechanism by which proximal tubule transport is regulated and highlights the clear importance of understanding the ligands and functional roles for ORs in the kidney.

Olfactory Receptor 78: A novel mechanism of blood pressure regulation

Olfr78 (MOR18-2) was initially identified as being expressed in whole kidney in 2009 [59]. Although an antibody against Olfr78 was successfully generated [26], it strongly cross-reacts with a mitochondrial protein in all other tissues tested – including the kidney. Therefore, a transgenic mouse model in which LacZ expression is driven by the Olfr78 promoter was used to identify cell types which normally express Olfr78. Using this tool, it was found that Olfr78 is found in the renal afferent arteriole [71] in the renal juxtaglomerular apparatus (JGA). Interestingly, the rat ortholog for Olfr78 (Olr59) was also found in whole glomeruli (Table 1) [63], suggesting that this localization pattern may be conserved across species. In addition, LacZ staining of non-renal tissues revealed that Olfr78 also localizes to small resistance vessels in a variety of vascular beds in the peripheral vasculature (Fig. 2). It is intriguing to note that both the JGA and the peripheral vasculature are classical sites known to play key roles in blood pressure regulation, and that the human ortholog of Olfr78 (hOR51E2) is also expressed at the RNA level in tissues consistent with these findings [62] (kidney, skeletal muscle, heart, etc.).

Although Olfr78 was initially an orphan receptor, an *in vitro* ligand screen revealed that it is a receptor for SCFAs – specifically, acetate and propionate [71] – and that the human ortholog of this receptor (hOR51E2) responds to the same two compounds. Although identifying OR orthologs across species is typically problematic, this OR appears to be uniquely well-conserved amongst mammalian species (with a clear ortholog in mice, rats, rabbits, elephants, horses and 5 species of primates [72]). As G_{olf} is not expressed in the afferent arteriole [59], Olfr78 in the afferent arteriole likely couples to G_s.

Intriguingly, SCFAs are present in the bloodstream primarily due to production by the gut microbiota [73]; bacteria in the gut produce SCFAs in large quantities (such that the concentration in the colonic lumen is ~100mM [73]), and then they are absorbed into the bloodstream in the low mM range (0.1–10mM [74–77]). The half maximal effective concentration (EC_{50}) of Olfr78 for acetate (2.35mM) and propionate (0.92mM) falls within this plasma range. SCFAs produced by the gut microbiota have been shown to play important roles in influencing several aspects of host physiology, including inflammatory responses and metabolism [75; 78].

As mentioned, Olfr78 localizes to two important sites of blood pressure control. One of these sites is the afferent arteriole. Here, renin - the rate-limiting step in the renin-angiotensin-aldosterone pathway - is stored and secreted into the bloodstream. Renin is responsible for the hydrolysis of angiotensinogen to angiotensin I, which is further cleaved to angiotensin II, a potent vasoconstrictor (Fig. 2). Because Olfr78 localizes to the renal afferent arteriole, it was investigated whether Olfr78 might mediate an increase in renin secretion in response to SCFAs. Indeed, in an *ex vivo* preparation it was demonstrated that

SCFAs induced renin release, and that this effect was dependent on Olfr78 [71]. Furthermore, in support of this, it was found that Olfr78 null animals had lowered plasma renin, and lowered baseline blood pressure [71] (Fig. 2). Thus, these findings present a novel pathway whereby activation of a sensory receptor, Olfr78, mediates changes in plasma renin and in blood pressure. It should be noted that some ORs have been shown to be mechanosensitive [79; 80]; however, it is unknown whether Olfr78 may be responding to mechanical (changes in blood flow?) as well as chemical stimuli.

Because Olfr78 also localizes to the peripheral vasculature, it was also determined whether SCFAs might also have an acute effect on vascular resistance, another important aspect of blood pressure control. Previous studies had reported that SCFAs can indeed induce vasodilation in isolated vessels [81–83]; to determine if there was an *in vivo* consequence of this vasodilation, SCFAs were delivered exogenously (intravenously) and blood pressure was measured. It was found that SCFA delivery caused a rapid, reproducible and dose-dependent hypotensive response. However, subsequent studies showed that this response is primarily due to activation of another SCFA receptor (Gpr41), whereas Olfr78 acts as a 'brake' on this response. Therefore, Olfr78 activation by SCFAs serves to increase blood pressure through two independent methods: increased renin release from the JGA and changes in in peripheral vascular resistance (Fig. 2). (The opposing actions of Olfr78 and Gpr41 on blood pressure regulation have been reviewed in detail: [84; 85]).

Conclusion

In conclusion, recent studies have highlighted novel and unexpected roles that sensory receptors, including ORs, play in a variety of tissues. As a key regulator of homeostasis, the kidney is a particularly intriguing location to employ such receptors, and recent studies have shown that ORs, taste receptors and other sensory GPRs are found in the kidney. Although there are a number of challenges to studying to ORs, it will be important for future studies to carefully explore and elucidate the novel roles that these receptors play in renal function.

Acknowledgements

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A. Canonical OR Signaling Pathway in the Olfactory Epithelium
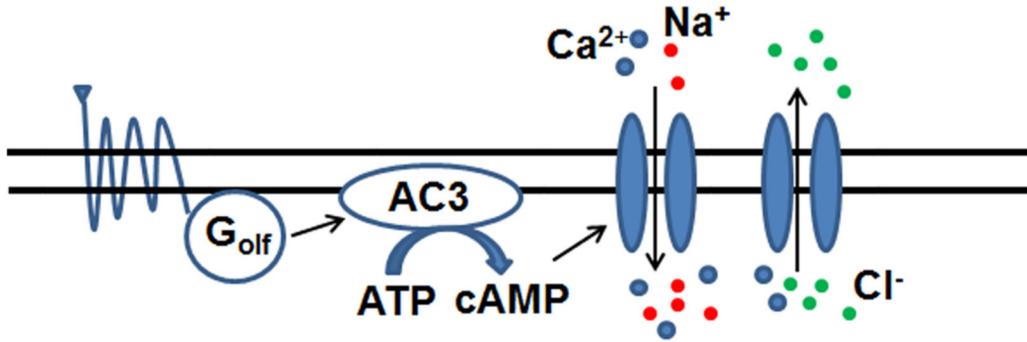
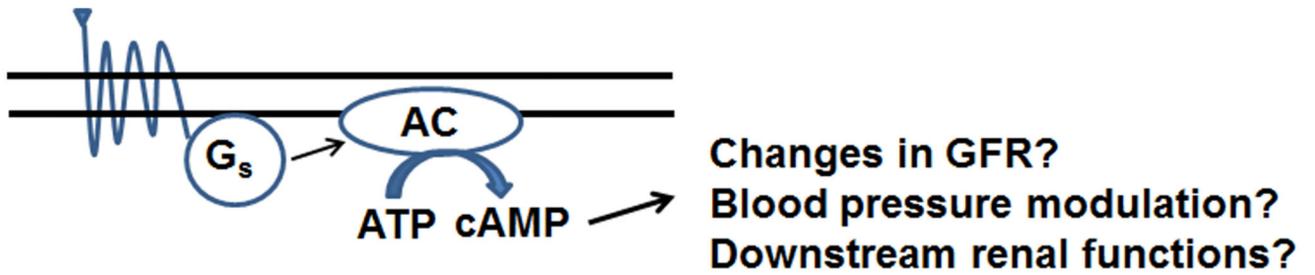## B. Potential OR Signaling Pathways in the Kidney

Figure 1.
Olfactory receptor (OR) signaling pathways. A) The canonical OR signaling pathway in the olfactory epithelium. OR-ligand binding activates $G_{olfactory}$ (G_{olf}) leading to increased cAMP via Adenylate Cyclase 3 (AC3) and the subsequent depolarization of olfactory sensory neurons. B) The potential OR signaling pathways in the kidney. As G_{olf} and AC3 are not ubiquitous in the nephron, it is likely that an activated renal OR binds a stimulatory G protein (G_s) leading to cAMP production by different adenylate cyclases and changes in renal function.
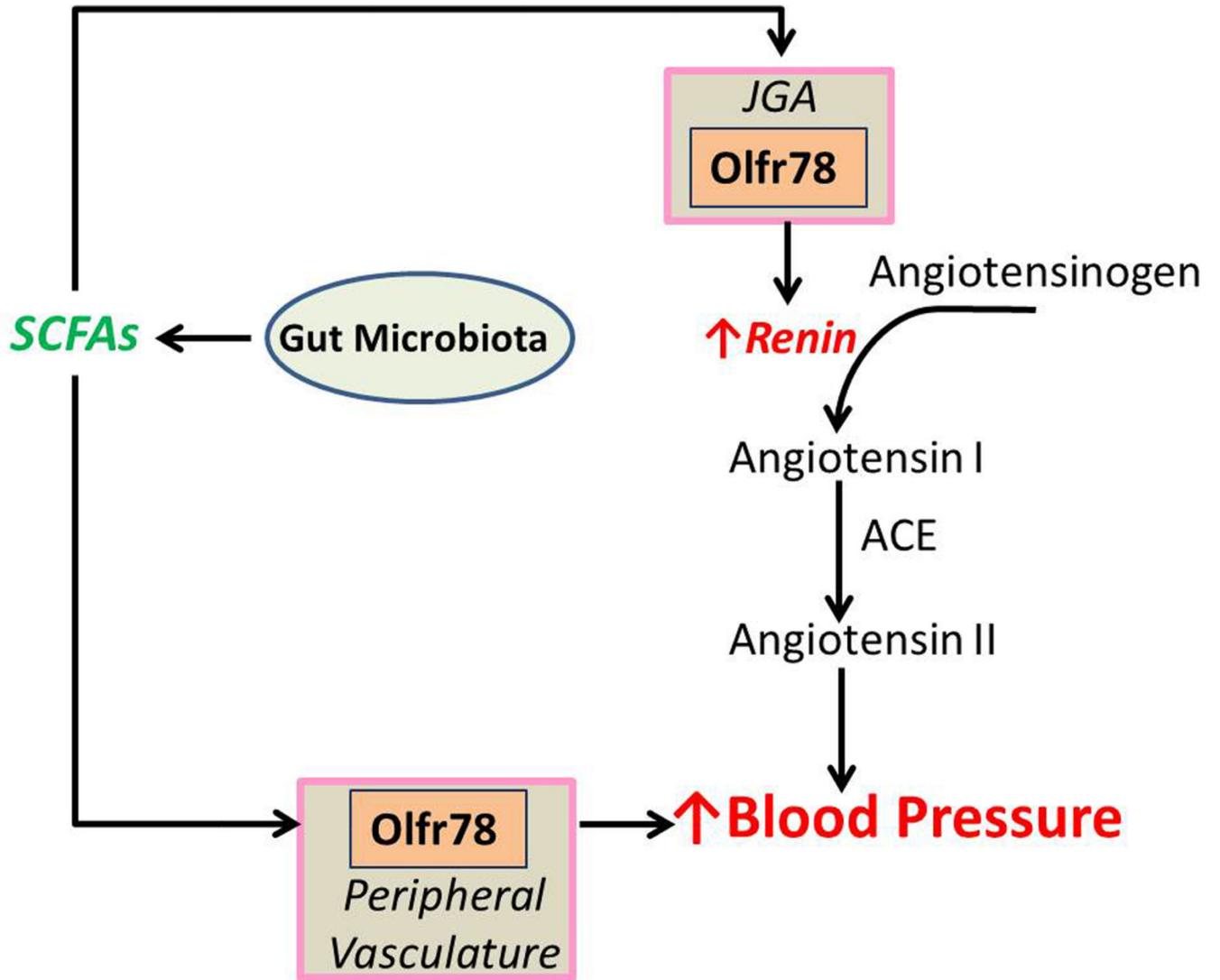
Figure 2.
Short chain fatty acids (SCFAs) produced by the gut microbiota activate Olfr78 in the both the renal juxtaglomerular apparatus (JGA) and peripheral vasculature. Activation of Olfr78 in the JGA leads to increased renin release. In the peripheral vasculature, activation of Olfr78 modulates a hypotensive response mediated by other SCFA receptors. In both cases, activation of Olfr78 leads to an increased blood pressure response.

Table I

Identified Renal Olfactory Receptors (ORs)

OR	Species	Method of Detection	Localization	Ligands	References
Olfr78	Mouse	RT-PCR Microarray	Afferent arteriole Isolated JG Cells	Short chain fatty acids	[59; 64] [61]
(Ortholog of Olr59 and OR51E2)					
Olr59	Rat	RNA-seq	Glomeruli	-	[63]
(Ortholog of Olfr78 and OR51E2)					
OR51E2	Human	RNA-seq	-	Propionate Acetate β-ionone Steroid hormones	[62; 86]
(Ortholog of Olfr78 and Olr59)					
Olfr90	Mouse	RT-PCR	Macula Densa	-	[59]
Olfr1392	Mouse	RT-PCR	-	-	[59]
Olfr1393	Mouse	RT-PCR	-	-	[59]
Olfr99	Mouse	RT-PCR	-	-	[59]
Olfr545	Mouse	RT-PCR	-	Sebacic acid*	[60; 87]
Olfr691	Mouse	RT-PCR	-	Short and medium chain fatty acids	[60; 68]
Olfr693	Mouse	RT-PCR	-	-	[60]
Olfr31	Mouse	RT-PCR	-	-	[60]
Olfr1426	Mouse	RT-PCR	-	-	[60]
Olfr95	Mouse	Microarray	Isolated JG Cells	-	[61]
Olfr796	Mouse	Microarray	Isolated JG Cells	-	[61]
Olfr1303	Mouse	Microarray	Isolated JG Cells	-	[61]

OR	Species	Method of Detection	Localization	Ligands	References
Olfr239	Mouse	Microarray	Isolated JG Cells	-	[61]
Olfr1200	Mouse	Microarray	Isolated JG Cells	-	[61]
Olfr373	Mouse	Microarray	Isolated JG Cells	-	[61]
Olfr558	Mouse	Microarray	Isolated JG Cells	-	[61]
Olr1104	Rat	RNA-seq	DCT	-	[63]
Olr1694	Rat	RNA-seq	S3, LDLIM, tAL, IMCD, Glomeruli	-	[63]
Olr560	Rat	RNA-seq	Entire nephron, Glomeruli	-	[63]
Olr63	Rat	RNA-seq	Glomeruli	-	[63]
OR10A2	Human	RNA-seq	-	-	[62]
OR1L8	Human	RNA-seq	-	-	[62]
OR2A1	Human	RNA-seq	-	-	[62]
OR2A42	Human	RNA-seq	-	-	[62]
OR2A7	Human	RNA-seq	-	-	[62]
OR2AG1	Human	RNA-seq	-	Amylbutyrate	[62; 88]
OR2T10	Human	RNA-seq	-	Maltyl isobutyrate, cinnamaldehyde, vanillin, terpinyl acetate and α-damascone	[62; 89]
OR51E1	Human	RNA-seq	-	Methyl valeric acid, valeric acid and isovaleric acid	[62; 90]
OR51I1	Human	RNA-seq	-	-	[62]
OR51I2	Human	RNA-seq	-	-	[62]

OR	Species	Method of Detection	Localization	Ligands	References
OR56B1	Human	RNA-seq	-	-	[62]
OR9A4	Human	RNA-seq	-	-	[62]

JG Cells, Juxtaglomerular cells; DCT, distal convoluted tubule; S3, third segment of proximal tubule; LDLIM, long descending limb of the loop of Henle in the inner medulla; tAL, thin ascending limb of the loop of Henle; IMCD, inner medullary collecting duct

*
Sebacic acid was initially reported as a ligand [87], but was not confirmed in a recent screen [60]