INTRODUCTION

Olfactory receptors (ORs), taste receptors (TRs), and photoreceptors/opsins (OPNs) have been primarily recognized for their key roles in smell, taste, and sight. However, recent studies have highlighted novel roles for these receptors in a variety of additional processes, including modulation of renal, cardiovascular, and pulmonary function (Dalesio et al., 2018). The great majority of TRs, and all OPNs and ORs, are G-protein-coupled receptors (GPCRs). In fact, ORs represent the largest family of GPCRs, with ~1000 receptors in mice and ~350 receptors in humans (Godfrey et al., 2004; Malnic et al., 2004). TRs belong to one of two GPCR families: type 1 (Tas1r) for sweet/umami taste, and type 2 (Tas2r) for bitter taste. ORs and TRs respond to chemical ligands, whereas OPNs are activated by photons. In addition to the visual photoreceptors, there are also non-visual photoreceptors that have been recently discovered: Opn3, Opn4, and Opn5.

The roles of these sensory GPCRs have been explored in a number of tissues beyond the eyes, nose, and tongue. For example, OR1D2 guides sperm to the egg during the fertilization process (Spehr et al., 2003), sweet TRs expressed in mouse pancreatic islets induce insulin secretion in vitro (Nakagawa et al., 2009), and Opn4 mediates blood vessel dilation (Sikka et al., 2014). The bladder is well known to express classical GPCRs, such as the β adrenergic receptors, which can respond to external stimuli to modulate urothelium function (Otsuka et al., 2008). Although other studies have reported the presence sensory GPCRs in bladder (Elliott et al., 2011; Uhlen et al., 2015; Weber et al., 2018; Yu et al., 2019), there has not yet been a systematic exploration of sensory GPCRs in the bladder. In this study, our goal was to systematically screen the bladder for ORs, TRs, and OPNs, in...
the hopes of beginning to uncover and understand the localization and function of sensory GPCRs in the bladder.

2 | METHODS

2.1 | Animals

All animal protocols were approved by the Johns Hopkins University Animal Care and Use Committee. All mice used in this study were C57Bl/6J and were fed ad libitum and housed on a 14–10 light–dark cycle.

2.2 | Taqman screen on bladder

C57BL/6J mice (two males, two females, 3 months of age) were euthanized in the morning between 10 a.m. and 12 p.m. by CO₂ inhalation. Whole bladders were harvested and homogenized in TRIzol reagent (Thermofisher 15596018), and RNA was extracted. RNA was then further processed using the Qiagen RNeasy Mini Kit with DNase digest protocol per manufacturer’s instructions. Fragment analysis was performed to ensure good RNA quality. Isolated RNA was reverse transcribed using the High Capacity cDNA Reverse Transcription Kit (Thermofisher 4368813). Quantitative PCR screening was performed using custom Taqman Low Density Array (TLDA) cards containing the probes noted in Table 1 (probes marked by an asterisk in Table 1 were not used in follow-up experiments because we found that the negative controls were not as reliable for these probes; instead, we used Opl1sw Mm01135620_g1, Olftr558 Mm01279850_m1, Opm3 custom probe APU66GD, Olftr78 Mm00628115_m1). For the TLDA card, ORs were selected based on the 40 most highly expressed human ORs as reported by Flegel et al. (2013). Of these 40 human ORs: 5 genes had no murine ortholog (NCBI) and thus were not included, two genes had two murine orthologs listed and these were both included, and one gene had a murine ortholog that was annotated as a pseudogene but it was included as it contains both a start and a stop site. In addition, we included 5 genes which our lab had previously observed as ectopically expressed (Olftr1392, Olftr1393, Olftr691, Olftr693, Olftr99, and Olftr31 (Pluznick et al., 2009; Rajkumar et al., 2014)), for a total of 43 ORs. The card additionally included all 35 murine bitter taste receptors as well as the taste receptors for umami and sweet, five opsin genes (including all three non-visual opsins), four G proteins associated with sensory signaling (Gnal, Gnat3, Gnat1, Gnat2), receptor transporting proteins 1–3, and GAPDH. One TLDA card was used per bladder sample. About 1 µg of bladder cDNA was added to each fill port (8 µg cDNA in total per card; ~21 ng per reaction). Cycling was performed using Taqman Fast Advanced Mastermix (Thermofisher 4444556).

2.3 | qRT-PCR for other organs

Three C57BL/6J male mice (4 months of age) were anesthetized with 10 mg/ml sodium pentobarbital and perfused with 1X PBS to remove blood. Organs collected were brain, colon, eye, heart, kidney, skeletal muscle, and tongue. RNA extraction was performed as described above, and reverse transcription was performed using the Qiagen Quantitect Reverse Transcription Kit (Qiagen cat# 205311). The top 10 sensory receptors detected in the bladder, along with negative control receptors which were not detected in the bladder, were screened via quantitative PCR using the Taqman Gene Expression Mastermix (Thermofisher 4369016). Mock reactions (no Reverse Transcriptase enzyme) were run as controls: 5 ng cDNA was used per reaction.

2.4 | Microdissection of mouse bladder and qRT-PCR

C57BL/6J mice (four males, four females, 3 months of age) were anesthetized with 10 mg/ml sodium pentobarbital and perfused with collagenase to ease separation of bladder layers. Whole bladders were harvested and cut in half, longitudinally. One half was used as the whole bladder control. The other half was microdissected in 1X PBS under a dissecting microscope. Fine forceps were used to peel off the urothelium. The remaining tissue was considered as the muscle layer. The tissues were homogenized in RLT buffer, and RNA was extracted following instructions from the Qiagen RNeasy Micro Kit (Qiagen cat# 74004). Quantitative PCR was performed using probes for luminal and muscle layers, as well as for the top 10 sensory receptors detected in the TLDA cards, following the same protocol mentioned above. Mock controls (no Reverse Transcriptase enzyme) were also performed for each probe. 5 ng cDNA was used per reaction.

2.5 | Statistics

All data are represented as mean ± standard deviation (SD). Statistical analyses were performed using Prism 8.2.1 by one-way ANOVA (multiple comparisons/tukey). A value of $p < 0.05$ was considered as significant. Because this is an exploratory study, p-values are descriptive rather than hypothesis testing.

3 | RESULTS

3.1 | Sensory GPCRs are found in murine bladder

Custom Taqman Low Density Array (TLDA) cards were used to screen reverse-transcribed RNA from C57BL/6J bladders
| Gene Name         | Assay ID         | Reference Sequence          |
|-------------------|------------------|----------------------------|
| **G Proteins**    |                  |                            |
| 1 Gnal            | Mm01258217_m1    | NM_010307.3;NM_177137.5    |
| 2 Gnat3           | Mm01165313_m1    | NM_001081143.1             |
| 3 GNAT1           | Hs00181100_m1    | NM_000172.3;NM_144499.2    |
| 4 GNAT2           | Hs00292542_m1    | XM_011541264.2;NM_005272.3 |
| **Olfactory Receptors (Olfr)** |            |                            |
| 1* Olfr78         | Mm00453733_s1    | NM_001168503.1;NM_130866.4 |
| 2 Olfr322         | Mm03040519_sH    | NM_207693.1                |
| 3 Olfr732         | Mm01322515_s1    | NM_146665.2                |
| 4* Olfr558        | Mm00530250_s1    | NM_147093.3                |
| 5 Olfr435         | Mm00730406_s1    | NM_146653.1                |
| 6 Olfr13          | Mm00455512_s1    | NM_146652.1                |
| 7 OLFR658         | Oc04252848_sH    | NM_001171477.1             |
| 8 Olfr211         | Mm00528861_s1    | NM_146912.1                |
| 9 Olfr177         | Mm00838183_s1    | NM_146996.2                |
| 10 Olfr410        | Mm00837649_s1    | NM_146707.1                |
| 11 Olfr56         | Mm01294180_s1    | NM_010999.2                |
| 12 Olfr90         | Mm01279749_s1    | NM_146477.2                |
| 13 Olfr1352       | Mm01173416_s1    | NM_147071.2                |
| 14 Olfr166        | Mm04211699_sH    | NM_147068.1                |
| 15 Olfr418        | Mm01294388_s1    | NM_146651.2                |
| 16 Olfr355        | Mm00730208_s1    | NM_146625.1                |
| 17 Olfr314        | Mm01353840_s1    | NM_001011760.2             |
| 18 Olfr91         | Mm00731552_s1    | NM_182714.2                |
| 19 Olfr287        | Mm01308734_s1    | NM_001011780.1             |
| 20 Olfr288        | Mm04214148_s1    | NM_001011733.2             |
| 21 Olfr411        | Mm00527201_s1    | NM_146709.2                |
| 22 Olfr618        | Mm00529874_s1    | NM_147047.2                |
| 23 Olfr273        | Mm00528191_s1    | NM_146824.1                |
| 24 Olfr267        | Mm00528927_s1    | NM_146920.2                |
| 25 Olfr71         | Mm00450916_s1    | NM_019486.1                |
| 26 Olfr15         | Mm00435446_s1    | NM_008762.2                |
| 27 Olfr26         | Mm02344389_s1    | NM_146783.2                |
| 28 Olfr933        | Mm00732053_s1    | NM_146441.1                |
| 29 Olfr646        | Mm01280303_s1    | NM_147056.1                |
| 30 Olfr57         | Mm00730842_s1    | NM_147041.2                |
| 31 Olfr714        | Mm01610019_s1    | NM_147033.2                |
| 32 Olfr11         | Mm03012560_s1    | NM_146542.2                |
| 33 Olfr873        | Mm01175052_s1    | NM_146561.1                |
| 34 Olfr308        | Mm00730170_s1    | NM_146621.1                |
| 35 Olfr935        | Mm00847580_s1    | NM_146746.1                |
| 36 Olfr1366       | Mm00525728_s1    | NM_146283.2                |
| 37 Olfr1428       | Mm00730594_s1    | NM_146678.2                |
| 38 Olfr1392       | Mm00836974_s1    | NM_146470.2                |

(Continues)
| Gene Name                | Assay ID                | Reference Sequence                        |
|-------------------------|-------------------------|-------------------------------------------|
| Olfr1393;Olfr10         | Mm00848749_g1           | NM_146471.1;NM_206822.1                   |
| Olfr691                 | Mm00529987_s1           | NM_147061.1                               |
| Olfr693                 | Mm00729330_s1           | NM_146453.2                               |
| Olfr99                  | Mm01280705_s1           | NM_146515.2                               |
| Olfr31                  | Mm01314539_s1           | NM_147027.2                               |
| Olfr545                 | Mm01279086_s1           | NM_146840.1                               |
| Opn4                    | Mm00443523_m1           | NM_001128599.1;NM_013887.2                |
| Opn1sw                  | Mm00432058_m1           | NM_007538.3                               |
| Opn5                    | Mm00710998_m1           | NM_181753.4                               |
| Opn1mw                  | Mm00433560_m1           | NM_008106.2                               |
| Opn3                    | Mm00438648_m1           | NM_010098.3                               |
| Rtp1                    | Mm01619091_m1           | NM_001004151.2                            |
| Rtp3                    | Mm00462169_m1           | NM_153100.2                               |
| Rtp2                    | Mm02374643_s1           | NM_001008230.3                            |
| Tas1r1                  | Mm00473433_m1           | NM_031867.2                               |
| Tas1r2                  | Mm00499716_m1           | NM_031873.1                               |
| Tas1r3                  | Mm00473459_g1           | NM_031872.2                               |
| Tas2r120                | Mm03014488_s1           | NM_207023.1                               |
| Tas2r109                | Mm0161497_g1            | NM_207017.1                               |
| Tas2r137                | Mm01167554_s1           | NM_001025385.1                            |
| Tas2r124                | Mm0161473_s1            | NM_207026.1                               |
| Tas2r108                | Mm00498514_s1           | NM_020502.1                               |
| Tas2r143                | Mm01700139_s1           | NM_001001452.1                            |
| Tas2r110                | Mm01160274_s1           | NM_199155.2                               |
| Tas2r135                | Mm01701729_s1           | NM_199159.1                               |
| Tas2r116                | Mm01160271_s1           | NM_053212.1                               |
| Tas2r129                | Mm03014501_s1           | NM_207029.1                               |
| Tas2r134                | Mm01701728_s1           | NM_199158.1                               |
| Tas2r126                | Mm01702063_s1           | NM_207028.1                               |
| Tas2r131                | Mm01702072_s1           | NM_207030.1                               |
| Tas2r105                | Mm00498502_s1           | NM_020501.1                               |
| Tas2r102                | Mm03014393_s1           | NM_199153.2                               |
| Tas2r104                | Mm01702013_s1           | NM_207011.1                               |
| Tas2r140                | Mm03011269_s1           | NM_021562.1                               |
| Tas2r125                | Mm01160225_s1           | NM_207027.1                               |
| Tas2r119                | Mm00498529_s1           | NM_020503.2                               |
| Tas2r136                | Mm00663741_s1           | NM_181276.1                               |
| Tas2r114                | Mm01702033_s1           | NM_207019.1                               |
| Tas2r106                | Mm01702023_s1           | NM_207016.1                               |
| Tas2r139                | Mm00663740_s1           | NM_181275.1                               |

(Continues)
TABLE 1  (Continued)

| Gene Name | Assay ID       | Reference Sequence   |
|-----------|----------------|----------------------|
| 24        | Tas2r118       | Mm01702043_s1        | NM_207022.1         |
| 25        | Tas2r115       | Mm0160239_s1         | NM_207020.1         |
| 26        | Tas2r103       | Mm0161465_s1         | NM_053211.1         |
| 27        | Tas2r144       | Mm01700149_s1        | NM_001001453.1      |
| 28        | Tas2r130       | Mm01701719_s1        | NM_199156.1         |
| 29        | Tas2r113       | Mm01702024_m1        | NM_207018.1         |
| 30        | Tas2r121       | Mm01702053_s1        | NM_207024.1         |
| 31        | Tas2r123       | Mm0167370_s1         | NM_207025.1         |
| 32        | Tas2r107       | Mm01701709_s1        | NM_199154.1         |
| 33        | Tas2r122       | Mm03039326_s1        | NM_001039128.1      |
| 34        | Tas2r117       | Mm04213039_s1        | NM_207021.1         |
| 35        | Tas2r138       | Mm01700131_s1        | NM_001001451.1      |

Control

| Gene Name | Assay ID       | Reference Sequence   |
|-----------|----------------|----------------------|
|           | Gapdh          | Mm99999915_g1        | NM_001289726.1      |

FIGURE 1  Novel G-protein coupled sensory receptors in murine bladder. mRNA expression of detected transcripts (30/94 receptors screened) in murine bladder was quantified by qRT-PCR using Taqman low density array cards. Data are represented as mean ± SD. N = 4. SD for Olfr57 = ±3.93E-05, Olfr1393 = ±7.78E-06, Olfr1428 = ±9.38E-06, Opn1mw = ±5.11E-06.
(two males, two females). Probes for the genes on each card are listed in Table 1 and described in the Methods, and include sensory GPCRs and accessory proteins. Of the 94 transcripts screened, 30 were detected in the bladder (Ct<36). In Figure 1, sensory receptors are arranged in descending order of expression in the bladder, relative to GAPDH. The top 10 transcripts (Ct<31) include two OPNs, three ORs, four bitter TRs, one sweet/umami TR, and the G protein for olfaction (Golf). The gene for the blue cone receptor, Opn1sw, had the highest expression on all four array cards. The sweet/umami TR, Tas1r3, had the second highest expression. Two short-chain fatty acid receptors that our lab has previously studied in the kidney, Olfr558 (Halperin Kuhns et al., 2019) and Olfr78 (Pluznick et al., 2013), were also detected. Although this screen was not powered to examine sex differences, there were no clear patterns of differences by sex. We subsequently confirmed the expression of the top 10 sensory GPCRs in a separate experiment (Figure 2). In future experiments, we focused on the receptors with the highest level of expression in the bladder.

3.2 | Sensory GPCRs are found in various organs

To determine if the sensory receptors expressed in the bladder are specific to the bladder, or, if they are broadly expressed, we...
performed a tissue qPCR screen. This screen included brain, colon, eye, heart, kidney, skeletal muscle, and tongue. We screened the top 10 bladder sensory receptors from the TLD cards: Opn1sw, Tas1r3, Olfr558, Opn3, Tas2r143, Tas2r135, Olfr99, Olfr78, Tas2r108, and Tas2r126 (Figure 3a-j). Tas1r1 was also included because it was the only other type 1 taste receptor detected in bladder (Figure 3k), and type 1 taste receptors function as dimers. Also included in this screen were two negative controls that were not detected in bladder: Opn4 and Tas1r2. Opn4 and Tas1r2 were also negative in the other tissues screened, with the exception of their respective positive control tissues: Opn4 was only detected in the eye, and Tas1r2 was detected only in the tongue (Figure 3l-m).

Of the sensory receptors found to be expressed in the bladder, all were expressed in a variety of tissues in addition to the bladder (and the eye or tongue). However, the distribution of each individual receptor was different. For example, Opn1sw had the highest expression in the eye, and had varied levels of expression in most other tissues, but was absent from the kidney. Tas1r3 was detected in nearly every tissue, but had little to no expression in skeletal muscle. By contrast, Tas2r143, Tas2r135, and Tas2r126 (Figure 3e,f,j) had higher expression in the bladder than in the other tissues examined. The highest Olfr78 expression was found in the colon, whereas the highest Olfr99 expression was found in the bladder and brain. Collectively, these data show that it is not uncommon to find a subset of sensory receptors outside of traditional sensory organs, with varying levels of expression.

3.3 Localization of top bladder sensory GPCRs within murine bladder

To determine the localization of the top bladder sensory receptors within the bladder, qPCR was performed on enriched bladder cell populations. Bladders were harvested from 8 C57BL/6J mice; half of the bladder served as the whole bladder control, whereas the other half was microdissected into the luminal fraction and the muscle fraction. First, qPCR was performed using probes for genes which we expected to be enriched in the luminal (epithelial Cadherin/ E-Cad and Uroplakin 1B/ Upk1b) or muscle layers (C-Kit and Alpha Smooth Muscle Actin/ α-SMA). These data confirmed that our microdissection protocol had significantly enriched each fraction as expected (Figure 4a); vascular Endothelial Cadherin/VE-Cad is an endothelial marker (endothelial cells are found in the suburothelium between the urothelium and muscle layers).

Next, we performed qPCR on these enriched cell fractions for the top 10 sensory receptors from the TLD cards, along with Tas1r1 (Figure 4b). We found Opn1sw to be the only receptor significantly enriched in the muscle fraction, although Olfr558 and Olfr78 trended toward higher expression in the muscle fraction. Olfr99 also showed no significant enrichment in either fraction. Tas1r3, Opn3, Tas2r143, Tas2r135, Tas2r108, Tas2r126, and Tas1r1 were significantly enriched in the luminal fraction. We did not observe any sex differences.
Additionally, we compared the top 30 sensory GPCRs from our study against RNASeq data from human bladder (Uhlen et al., 2015) (Figure 5), and noted a few receptors that were expressed in both human and murine bladder including: Tas1r3, Olftr558/OR51E1, Opn3, Tas2r135/TAS2R60, and Olftr78/OR51E2. Among these, Opn3 had the highest expression in human bladder.

4 | DISCUSSION

In this study, we systemically examined the expression of sensory GPCRs in the bladder for the first time. We found that of the 94 transcripts screened, 30 were expressed in the bladder. The most highly expressed transcripts included two OPNs, three ORs, and five TRs, and these GPCRs exhibited a widespread but varied expression in other tissues. Within the bladder, most of these GPCRs were enriched in the luminal fraction.

4.1 | Other reports of sensory GPCRs in bladder

Although ours is the first systemic examination of sensory receptors in the bladder, there are other reports which have examined individual TRs or ORs in the bladder. For example, Elliott, et al reported that sweet TRs (Tas1r2 and Tas1r3 dimer) are expressed in human and rat urothelium on the protein level, and suggested they may play a role in bladder contraction (Elliott et al., 2011). While our study also saw expression of Tas1r3 in murine bladder, we instead observed co-expression of Tas1r1 (Tas1r1 and Tas1r3 would constitute the umami TR). Localization of Tas1r3 expression to the rat urothelium by Elliott, et al. is in agreement with our data showing significant enrichment of Tas1r3 in the luminal fraction of mouse bladder. The differences between our findings may reflect species differences, or the different methodologies used. In a separate study, Zhai, et al. reported that 19 bitter TRs were detected in mouse detrusor muscle (Zhai et al., 2016). However, the bitter TRs with the highest expression in this study were not detected in our screen, and the bitter TRs found in our screen were found at relatively low levels in their study. Notably, we screened whole bladder, whereas Zhai et al screened detrusor muscle, and this may account for some of these differences – especially given that we see enrichment of bitter TRs in the luminal fraction. Finally, we are aware of one study which reported expression of an OR in human bladder (with upregulated expression in bladder cancer): OR10H1 (Weber et al., 2018). This OR is not evolutionarily conserved (Niimura et al., 2014) and
thus its murine orthologs are uncertain. However, the putative mouse orthologs, Olfr239 and Olfr55, were not included in our screen and have not been reported in mouse bladder. While we performed qPCR to collect data from mouse tissue only, there is a study that performed RNA sequencing on mouse and human bladder tissue (Yu et al., 2019). In comparison to our data, Yu and others only detected the expression of three sensory GPCRs (Opn1sw, Opn3, Tas1r3) in mouse bladder and three sensory GPCRs in human bladder (Opn3, OR51E1/Olfr558, and OR51E2/Olfr78). Notably, this single-cell sequencing data also indicate that Opn3 may be more highly expressed in human bladder as compared with mouse. Uhlen et al. (2015) performed RNA sequencing on several human tissues including bladder and detected the expression of the following sensory GPCRs that were also detected in our screen: Tas1r3, Olfr558/OR51E1, Opn3, Tas2r135/TAS2r60, Olfr78/OR51E2, Gnal, Tas2r137, Olfr288/OR10A1, Tas1r1, Olfr15/OR2C1, and Olfr177/OR5K2. Though not bladder specifically, other tissues within close proximity, such as the urethra, have been shown to also express sensory GPCRs, specifically bitter TRs (Kummer & Deckmann, 2017).

In our study, we report that Opn1sw and Opn3 are expressed in the murine bladder. It is not yet known how these opsins are activated in vivo: does light naturally reach Opn1sw or Opn3 in the bladder? We know that the short-wave photoreceptor, Opn1sw, is activated by wavelengths in the blue light range. A study in 2018 demonstrated that blue light induces vasorelaxation via Opn3 and Opn4, implying that Opn3 is indeed activated by blue light in vivo. However, we should note that while most groups report that blue light activates Opn3 (Barreto Ortiz et al., 2018; Nayak et al., 2020; Regazzetti et al., 2018), whereas at least one group reports that it may not (Ozdeslik et al., 2019). Another possibility is that these opsins may have a light-independent role (Leung & Montell, 2017) – it would be intriguing to explore whether some opsins may also be activated by a chemical ligand, or by mechanotransduction. Moving forward, it will be key to understand the mechanism of activation for opsins in the bladder.

Although we do not yet have enough data to speculate on the functional role of specific sensory GPCRs in the bladder, we can draw from the existing literature of sensory GPCRs in other tissues to intuit potential function roles. For example, several studies have shown that some sensory GPCRs (including Olfr78 (Pluznick et al., 2013) and Olfr558 (Halperin Kuhns et al., 2019), both of which are found in murine bladder) are activated by bacterial metabolites. Thus, it is tempting to speculate that these receptors may be activated to modulate bladder contraction or pain mechanisms in conditions such as cystitis. In future studies, it will be critical to examine the functional role of each of these novel sensory GPCRs, and to understand how signaling of these GPCRs may influence bladder function in health and disease.

4.2 | Limitations

There are several limitations to our study. First, our analysis is focused on RNA, and RNA expression is not necessarily indicative of functional protein. In future studies, it will be important to look at both protein and at function. Conversely, a relatively low level of expression on the RNA level does not necessarily mean that the GPCR does not play a key role in bladder function: for example, if a GPCR is expressed only in a minority cell type, then relative abundance by whole bladder PCR would be low. Thus, GPCRs which are found at low or even absent levels of expression may still play significant roles in bladder function. Finally, we acknowledge that there may be species differences in expression of these sensory GPCRs, and this will be important to examine going forward.

ACKNOWLEDGMENT

We acknowledge the members of the Pluznick lab, especially Dr. Nathan Zaidman, for helpful discussions.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTION

T.A.S., D.E.B., and J.L.P. conceived these studies. T.A.S. and B.N.M. performed experiments. T.A.S., B.N.M., A.M., D.E.B., J.J.D., and J.L.P. analyzed data. T.A.S. and J.L.P. wrote the manuscript; T.A.S., B.N.M., A.M., D.E.B., J.J.D., and J.L.P. edited and approved the manuscript.

ORCID

Jennifer L. Pluznick https://orcid.org/0000-0003-3621-2665

REFERENCES

Barreto Ortiz, S., Hori, D., Nomura, Y., Yun, X., Jiang, H., Yong, H., Chen, J., Paek, S., Pandey, D., Sikka, G., Bhatta, A., Gillard, A., Stepan, J., Kim, J. H., Adachi, H., Barodka, V. M., Romer, L., An, S. S., Shimoda, L. A., … Berkowitz, D. E. (2018). Opsin 3 and 4 mediate light-induced pulmonary vasorelaxation that is potenti- ated by G protein-coupled receptor kinase 2 inhibition. American Journal of Physiology. Lung Cellular and Molecular Physiology, 314, L93–L106. https://doi.org/10.1152/ajplung.00091.2017

Dalesio, N. M., Barreto Ortiz, S. F., Pluznick, J. L., & Berkowitz, D. E. (2018). Olfactory, taste, and photonic sensory receptors in non-sensory organs: It just makes sense. Frontiers in Physiology, 9, 1673.

Elliott, R. A., Kapoor, S., & Tincello, D. G. (2011). Expression and distribution of the sweet taste receptor isoforms T1R2 and T1R3 in human and rat bladders. Journal of Urology, 186, 2455–2462. https://doi.org/10.1016/j.juro.2011.07.083

Flegel, C., Manteniotis, S., Osthold, S., Hatt, H., & Gisselmann, G. (2013). Expression profile of ectopic olfactory receptors
Pluznick, J. L., Zou, D. J., Zhang, X., Yan, Q., Rodriguez-Gil, D. J., Eisner, C., Wells, E., Greer, C. A., Wang, T., Firestein, S., Schnerrmann, J., & Caplan, M. J. (2009). Functional expression of the olfactory signaling system in the kidney. Proceedings of the National Academy of Sciences of the United States of America, 106, 2059–2064. https://doi.org/10.1073/pnas.0812859106

Rajkumar, P., Aisenberg, W. H., Acres, O. W., Protzko, R. J., & Pluznick, J. L. (2014). Identification and characterization of novel renal sensory receptors. PLoS One, 9, e111053. https://doi.org/10.1371/journal.pone.0111053

Regazzetti, C., Sormani, L., Debayle, D., Bernerd, F., Tulic, M. K., De Donatis, G. M., Chignon-Sicard, B., Rocchi, S., & Passeron, T. (2018). Melanocytes Sense Blue Light and Regulate Pigmentation through Opsin-3. The Journal of Investigative Dermatology, 138, 171–178. https://doi.org/10.1016/j.jid.2017.07.833

Sikka, G., Hussmann, G. P., Pandey, D., Cao, S., Hori, D., Park, J. T., Steppan, J., Kim, J. H., Barodka, V., Myers, A. C., Santanam, L., Nyhan, D., Halushka, M. K., Koehler, R. C., Snyder, S. H., Shimoda, L. A., & Berkowitz, D. E. (2014). Melanopsin mediates light-dependent relaxation in blood vessels. Proceedings of the National Academy of Sciences of the United States of America, 111, 17977–17982. https://doi.org/10.1073/pnas.1420258111

Spehr, M., Gisselmann, G., Poplawski, A., Rifflé, J. A., Wetzell, C. H., Zimmer, R. K., & Hatt, H. (2003). Identification of a testicular odorant receptor mediating human sperm chemotaxis. Science, 299, 2054–2058. https://doi.org/10.1126/science.1080376

Uhlen, M., Fagerberg, L., Hallström, B. M., Lindskog, C., Oksvold, P., Mardinoglu, A., Sivertsson, A., Kampf, C., Sjostedt, E., Asplund, A., Olsson, I., Edlund, K., Lundberg, E., Navani, S., Szegyarto, C.-A.-K., Odeberg, J., Djureinovic, D., Taken, J. O., Hober, S., … Ponten, F. (2015). Tissue-based map of the human proteome. Science, 347(6220), 1260419. https://doi.org/10.1126/science.1260419

Weber, L., Schulz, W. A., Philippou, S., Eckardt, J., Ubrig, B., Hoffmann, M. J., Tannapfel, A., Kalbe, B., Gisselmann, G., & Hatt, H. (2018). Characterization of the olfactory receptor OR10H1 in human urinary bladder cancer. Frontiers in Physiology, 9, 456. https://doi.org/10.3389/fphys.2018.00456

Yu, Z., Liao, J., Chen, Y., Zou, C., Zhang, H., Cheng, J., Liu, D., Li, T., Zhang, Q., Li, J., Yang, X., Ye, Y., Huang, Z., Long, X., Yang, R., & Mo, Z. (2019). Single-cell transcriptomic map of the human and mouse bladders. Journal of the American Society of Nephrology, 30, 2159–2176. https://doi.org/10.1681/ASN.2019040335

Zhai, K., Yang, Z., Zhu, X., Nyirimigabo, E., Mi, Y., Wang, Y., Liu, Q., Man, L., Wu, S., Jin, J., & Ji, G. (2016). Activation of bitter taste receptors (tas2rs) relaxes detrusor smooth muscle and suppresses overactive bladder symptoms. Oncotarget, 7, 21156–21167. https://doi.org/10.18632/oncotarget.8549

How to cite this article: Smith TA, Moore BN, Mataso A, Berkowitz DE, DeBerry JJ, Pluznick JL. Identification of novel bladder sensory GPCRs. Physiol Rep. 2021;9:e14840. https://doi.org/10.1484/phy2.14840

These citations are based on the references in the original document. The full references are provided in the markdown text following the bibliography section.