Chemosensation in Nontraditional Locations

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I have no disclosures relevant to this work.

Ectopic expression?

Nomotopic	νόμος(law, custom) + τόπος(place): occurring at the usual place “a biological event or process occurring in the normal/usual location or position in the body”
Ectopic	ἐκ(out) + τόπος(place): out-of-the-place “a biological event or process occurring in an abnormal location or position in the body”
Ecnomotopic	ἐκ(out) + νόμος(law, custom) + τόπος(place): out-of-the-usual(conventional)-place

Credit: Antonella Di Pizio
Leibniz-Institute for Food Systems Biology at the Technical University of Munich

Ecnomotopic Expression

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Chemosensation in Nontraditional Locations

?

Nomenclature

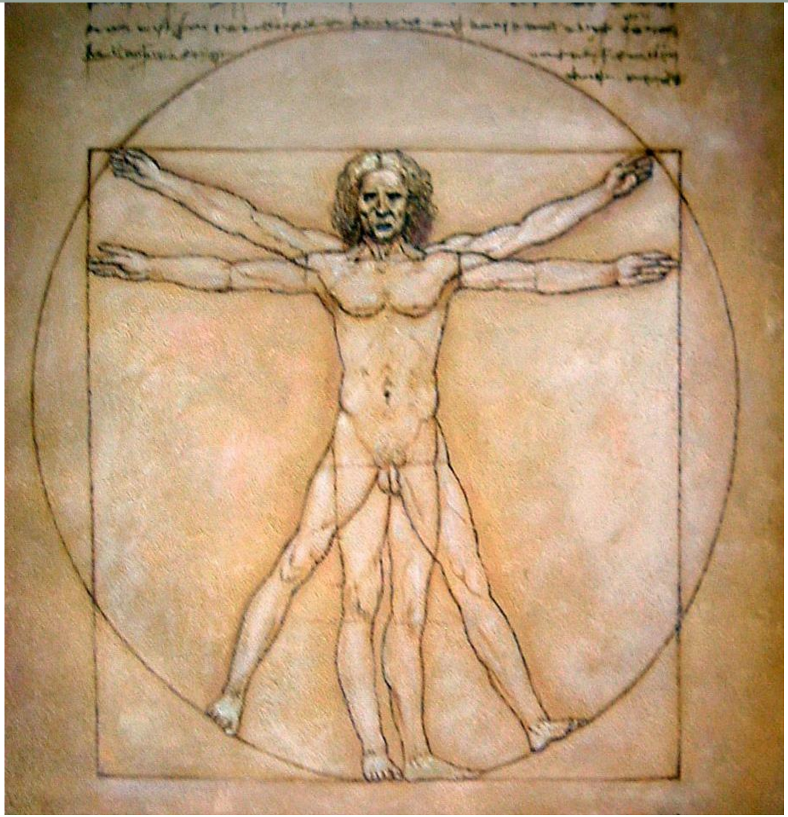
Credit: Antonella Di Pizio

Leibniz-Institute for Food Systems Biology at the Technical University of Munich

Ecnomotopic Expression of Chemosensory Receptors

- Olfactory receptors are involved in physiological processes in muscle, sperm, GI tract, cardiovascular system, kidney, and skin

- Taste receptors play important functions in airway smooth muscle, bladder, spinal column, immune system, and GI tract



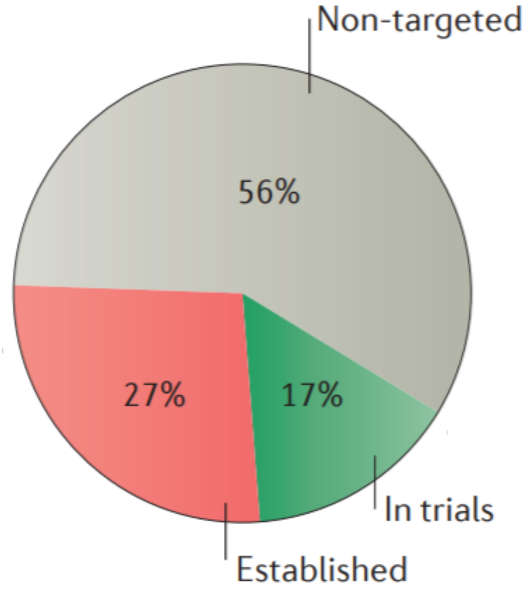
- Naturally occurring metabolites are often found to be ligands for these sensory receptors

- Opsins play roles in blood vessels, skin, adipose, and airway smooth muscle

Ecnomotopic Expression of Chemosensors: An Opportunity

34% of FDA-approved drugs target G-protein coupled receptors (GPCRs)

<u>GPCRs</u>



Includes opsins and taste receptors, but <u>not</u> olfactory receptors…

Including ORs:
76% non-targeted

Hauser, et al Nature Rev Drug Discovery 2017

Olfactory Receptors: Orthologs?

Largest gene family in the genome

Research

Extreme expansion of the olfactory receptor gene repertoire in African elephants and evolutionary dynamics of orthologous gene groups in 13 placental mammals

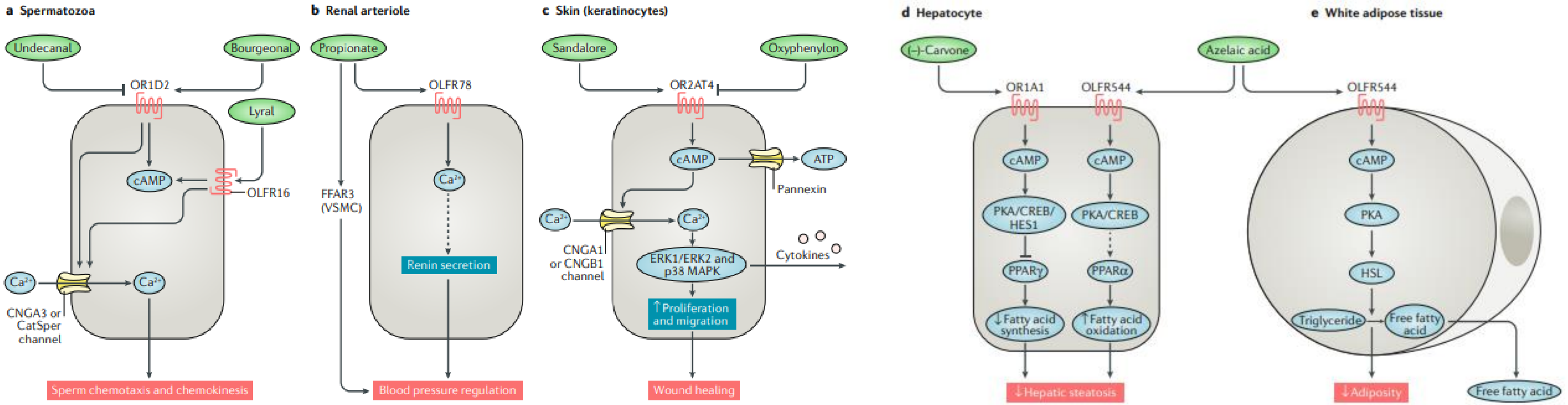
Yoshihito Niimura,[1,2] Atsushi Matsui,[1,2] and Kazushige Touhara[1,2]

[1]*Department of Applied Biological Chemistry, Graduate School of Agricultural and Life Sciences, The University of Tokyo, Tokyo 113-8657, Japan;* [2]*ERATO Touhara Chemosensory Signal Project, JST, The University of Tokyo, Tokyo 113-8657, Japan*

Regarding OR51E1 and OR51E2: “Remarkably, both of them are ubiquitously expressed in various tissues. Recently, Flegel and colleagues investigated the expression of human OR genes in 16 different nonolfactory tissues (Flegel et al. 2013). They found that OR51E1 and OR51E2 are expressed in 13 and 12, respectively, of the 16 nonolfactory tissues and they are the two most broadly expressed human OR genes among those examined.”

Human	Mouse	Rat
OR51E1	Olfr558	Olr63
OR51E2	Olfr78	Olr59
OR6B1	Olfr449	Olr811

Olfactory Receptors: Ecnomotopic Roles

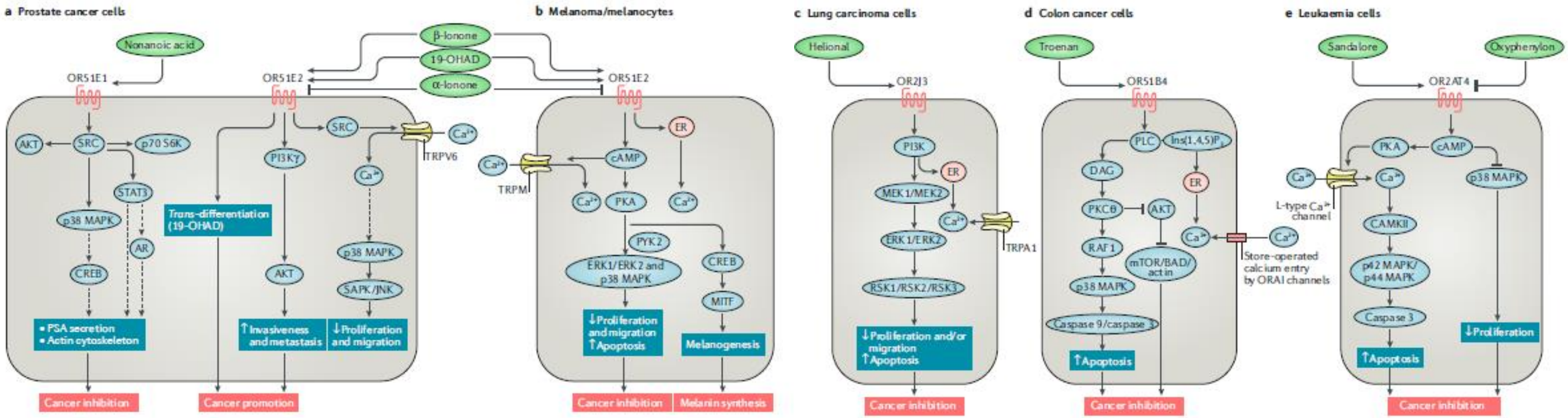


OR… = human
Olfr… = mouse

Lee, Depoortere and Hatt, *Nature Reviews Drug Discovery*, 2019.

Olfactory Receptors and cancer

OR51E2 is aka PSGR (prostate-specific GPCR)



OR… = human
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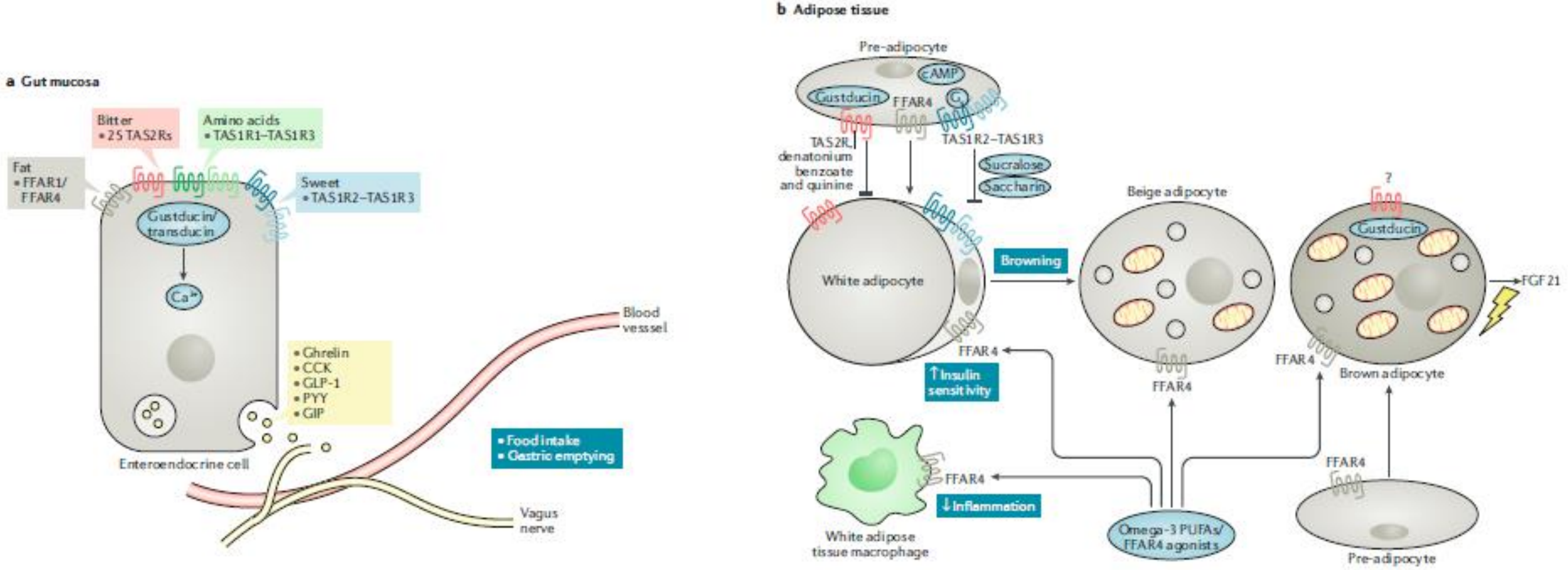
Lee, Depoortere and Hatt, *Nature Reviews Drug Discovery*, 2019.

Taste Receptors

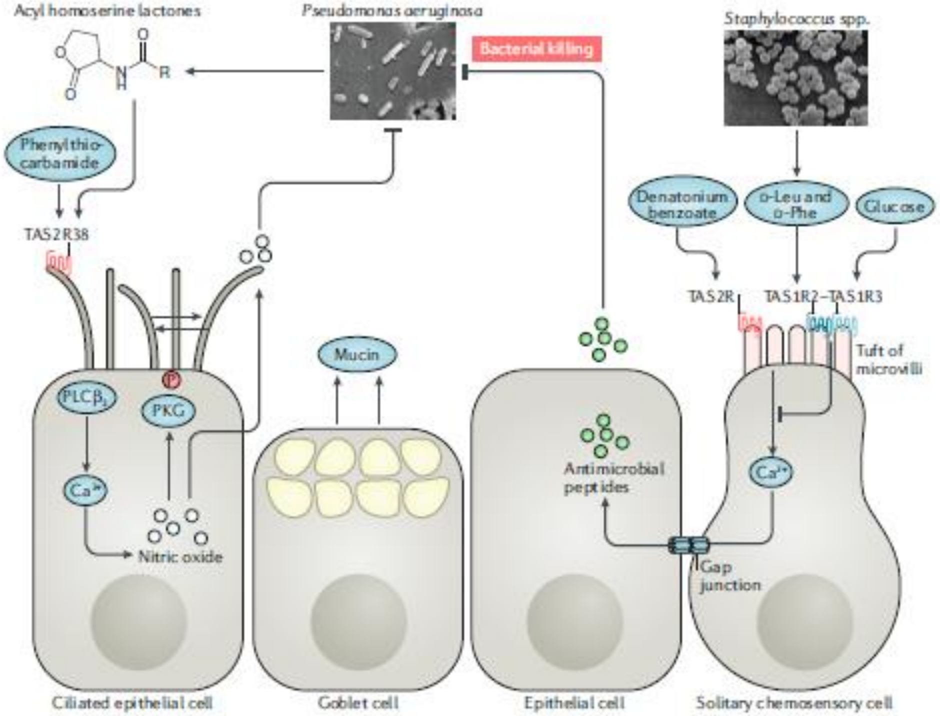
T1Rs (sweet, umami) and T2Rs (bitter) are conserved among vertebrates.



FFAR4 = not strictly a taste receptor

Lee, Depoortere and Hatt, *Nature Reviews Drug Discovery*, 2019.

Taste Receptors



Lee, Depoortere and Hatt, *Nature Reviews Drug Discovery*, 2019.

Opsins

TABLE 1 | Selected taste, olfactory, and photoreceptors with suggested functions outside of their natural sensory organ in different animal species.

Name	Alternative names	Respiratory system	GI system	GU system	CV system	CNS	Immune system	Skin	Adipose tissue	Retina (non-visual)	Others	References
PHOTORECEPTORS												
Opsin 1-S	Short-wavelength							H, Re				Tsutsumi et al., 2009; Fulgione et al., 2014; Haltaufderhyde et al., 2015
Opsin 1-LM	Long/medium wavelength							H				Tsutsumi et al., 2009
Opsin 2	Rhodopsin			H, M				H, C			F (larvae)	Tsutsumi et al., 2009; Shen et al., 2011; Bellono et al., 2013, 2014; Haltaufderhyde et al., 2015; Pérez-Cerezales et al., 2015; Buscone et al., 2017
Opsin 3	Encephalopsin, panopsin	H		H, M	H, M, R	M	H	H		H		Blackshaw and Snyder, 1999; White et al., 2008; Haltaufderhyde et al., 2015; Pérez-Cerezales et al., 2015; Buscone et al., 2017; Barreto Ortiz et al., 2018; Regazzetti et al., 2018
Opsin 4	Melanopsin			H, M	H, M, R	H, T		A	H, M	H, P, M, R,T		Provencio et al., 1998; Rollag et al., 2003; Fernandes et al., 2012; Sikka et al., 2014; Pérez-Cerezales et al., 2015; Nissil et al., 2017; Ondrusova et al., 2017; Barreto Ortiz et al., 2018

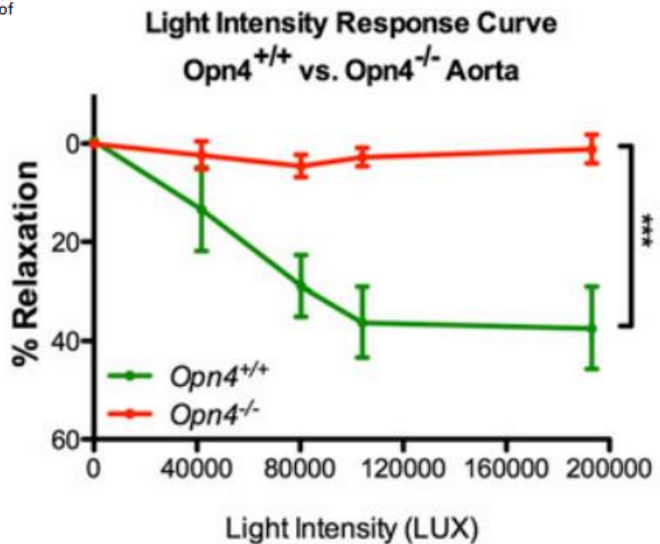
Dalesio, Ortiz, Pluznick and Berkowitz. *Frontiers in Physiology*, 2018.

Opsins

Melanopsin mediates light-dependent relaxation in blood vessels

Gautam Sikka[a], G. Patrick Hussmann[b], Deepesh Pandey[a], Suyi Cao[a], Daijiro Hori[c], Jong Taek Park[a], Jochen Steppan[a], Jae Hyung Kim[a], Viachaslau Barodka[a], Allen C. Myers[d], Lakshmi Santhanam[a,e], Daniel Nyhan[a], Marc K. Halushka[f], Raymond C. Koehler[a], Solomon H. Snyder[f,1], Larissa A. Shimoda[g], and Dan E. Berkowitz[a,e,1]

[a]Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University, Baltimore, MD 21287; [b]Department of Neuroscience, Johns Hopkins University, Baltimore, MD 21205; [c]Department of Surgery, Johns Hopkins University, Baltimore, MD 21287; [d]Department of Allergy and Immunology, Johns Hopkins University, Baltimore, MD 21224; [e]Department of Biomedical Engineering, Johns Hopkins University, Baltimore, MD 21205; [f]Department of Pathology, Johns Hopkins University, Baltimore, MD 21287; and [g]Division of Pulmonary Medicine, Johns Hopkins University, Baltimore, MD 21224



Stay tuned…

Enrique Saez and *Catia Sternini* – Intestinal bitter taste receptors
George Kyriazis – Pancreatic β-cell sweet taste receptor
John McLaughlin – Sensory signaling affects on appetite
Mark Lyte – Host-microbial interactions

Challenges in the field

Moving beyond cataloging ecnomotopic expression: identifying functional roles.

<u>Challenges to overcome</u>*:*

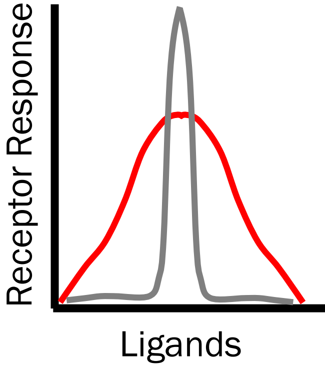
Functional human orthologs for rodent olfactory receptors.

Or, you can use human cell lines – but then we need cell lines that faithfully recapitulate physiology and pathophysiology.

Many sensory receptors are orphans: need to identify <u>ligands</u>

when we do identify ligands, some ORs/TRs are "widely tuned."

→identify physiologically relevant ligands



Reliable antibodies are scarce

Need better tools: floxed animals, <u>antagonists</u>.

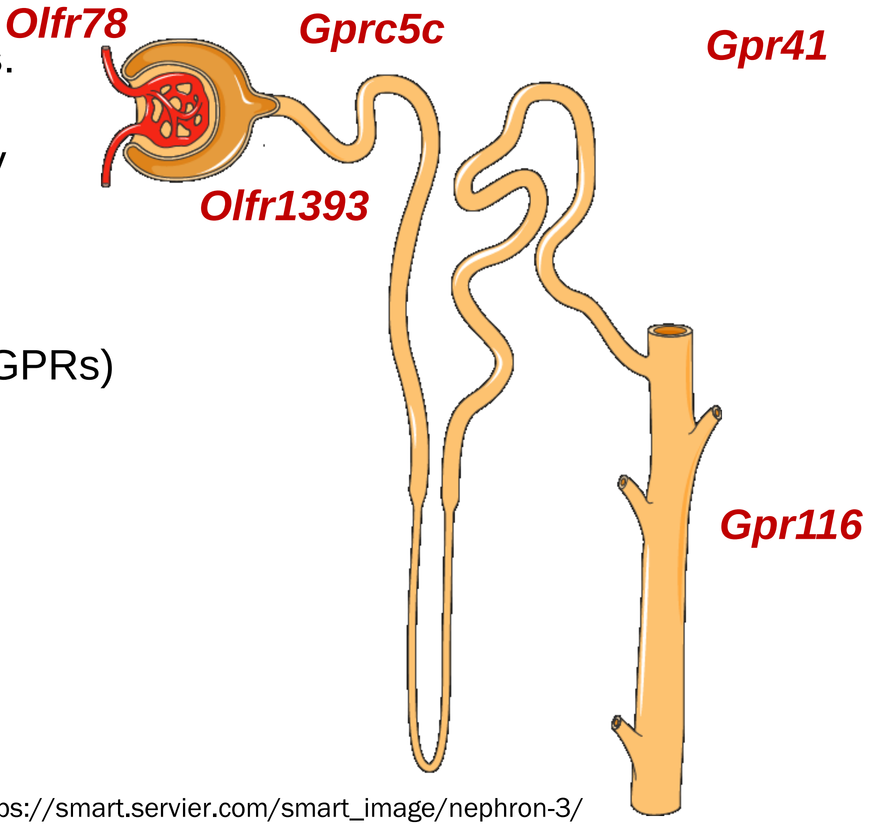
Downstream signaling?

Which “Novel” GPCRs are Found in the Kidney?

- The kidney’s job is to maintain homeostasis.
- To date, we have identified multiple sensory receptors in the <u>kidney</u>, including:
  - 18 olfactory receptors
  - 11 taste receptors
  - 76 (non-olfactory) orphaned GPCRs (GPRs)

(*PNAS 2009; PLoS One 2014; AJP-Renal 2019*)

- **<u>What do they do?</u>** (That is, what is the physiological role of each receptor?)



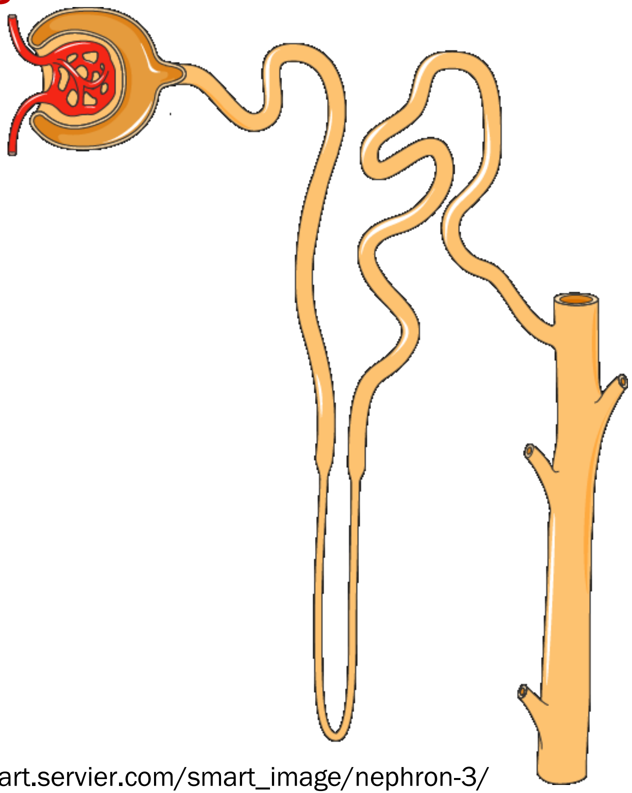
https://smart.servier.com/smart_image/nephron-3/

What does Olfr78 do in the kidney?

What is the physiological role of Olfr78?

Q1: Where is it found?

Q2: What is it activated by?
(i.e., what is the ligand?)

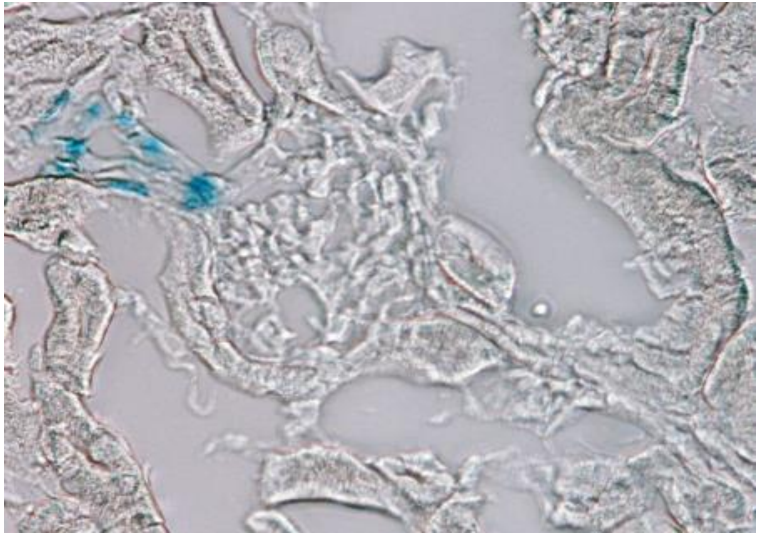


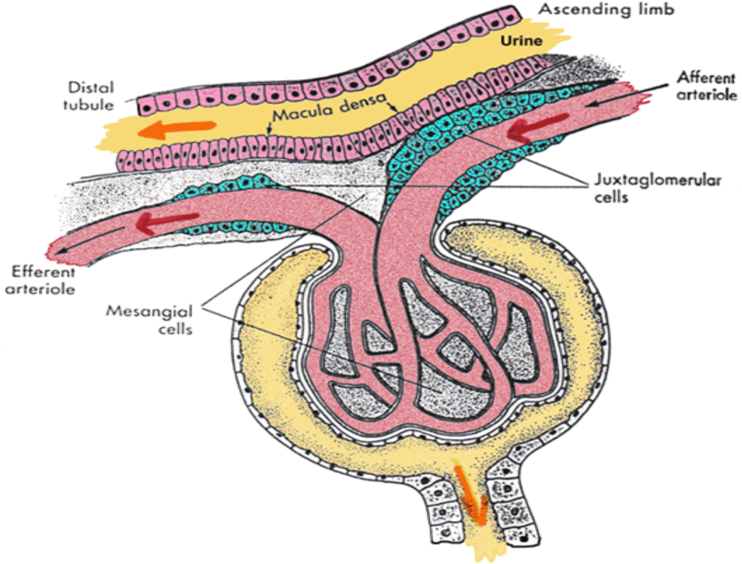
https://smart.servier.com/smart_image/nephron-3/

Olfr78: Localization

Olfr78 LacZ Reporter Gene

renal afferent arteriole (100X)



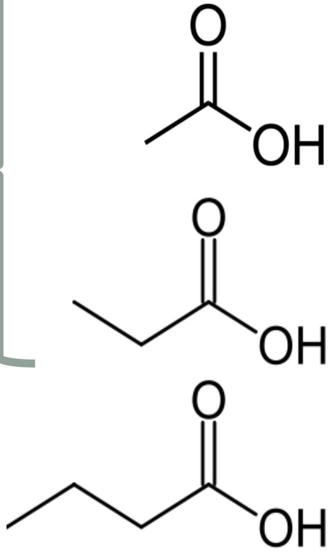


PNAS 2013

Olfr78: Ligands

Short chain fatty acids (SCFAs) are short carboxylic acids which are present in the bloodstream due to metabolic production by <u>gut microbes</u>.

Ligands for <u>**Olfr78**</u> (mouse), OR51E2 (human)



Acetate

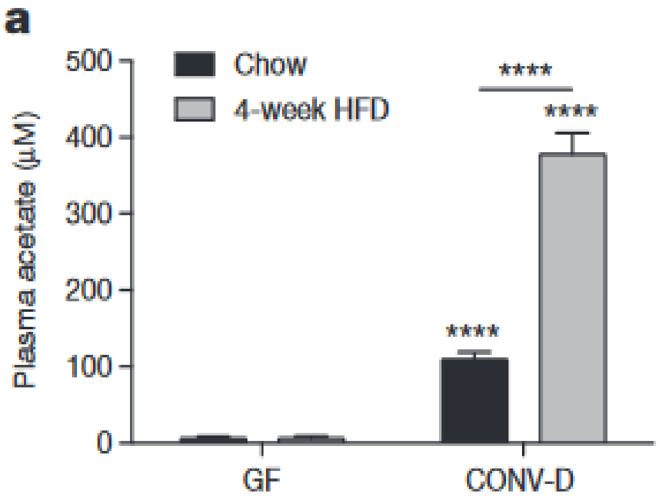
Propionate

Butyrate

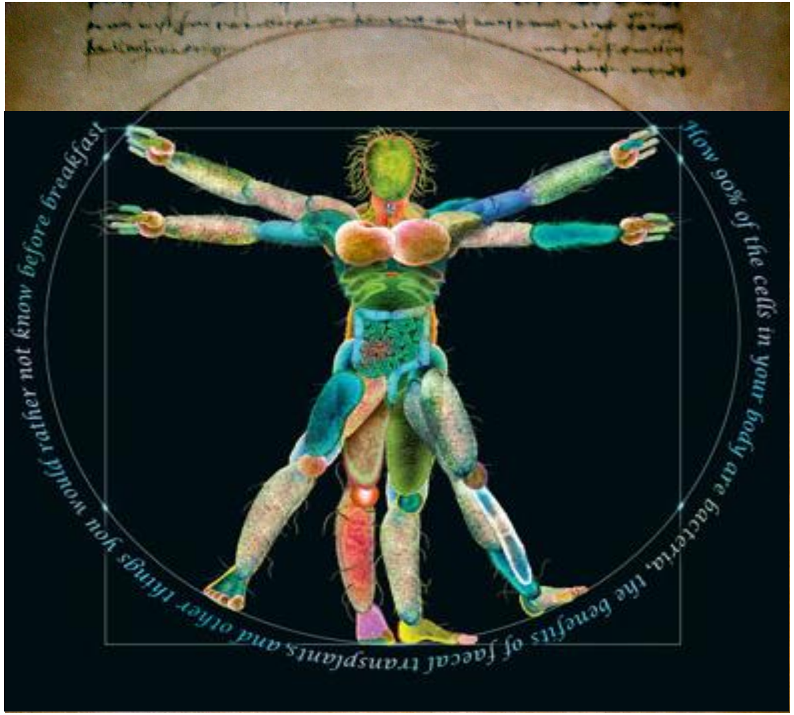
PNAS 2013
Sci Rep 2016

Short Chain Fatty Acids (SCFAs)

Short chain fatty acids (SCFAs) are short carboxylic acids which are present in the bloodstream due to metabolic production by gut microbes.



Perry, et al. Nature 2016



The Economist, Microbes Maketh Man, Aug. 2012

What does Olfr78 do in the Kidney?

What is the physiological role of Olfr78?

Q1: Where is it found?

Renal afferent arteriole

Q2: What is it activated by?

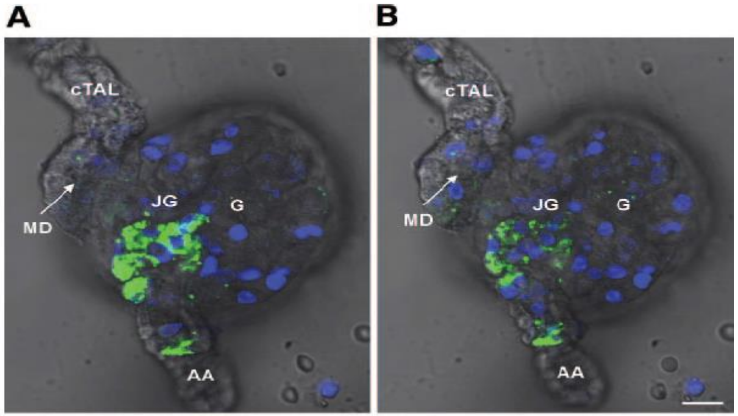
(i.e., what is the ligand?)

Short chain fatty acids

Can SCFAs modulate renin release via Olfr78?

Glomeruli/cTAL-MD preparations with attached afferent arteriole/glomeruli

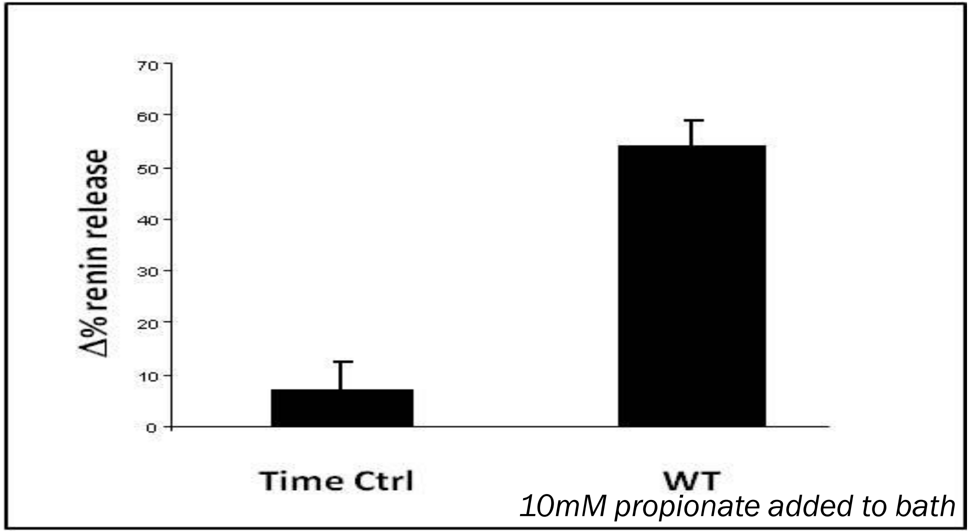
Stain renin granules with quinacrine



Add agonist to bath, and measure the change in quinacrine fluorescence as an index of renin release.

Vargas, et al. JASN 2009

Effect of Propionate on Renin Release in WT mice

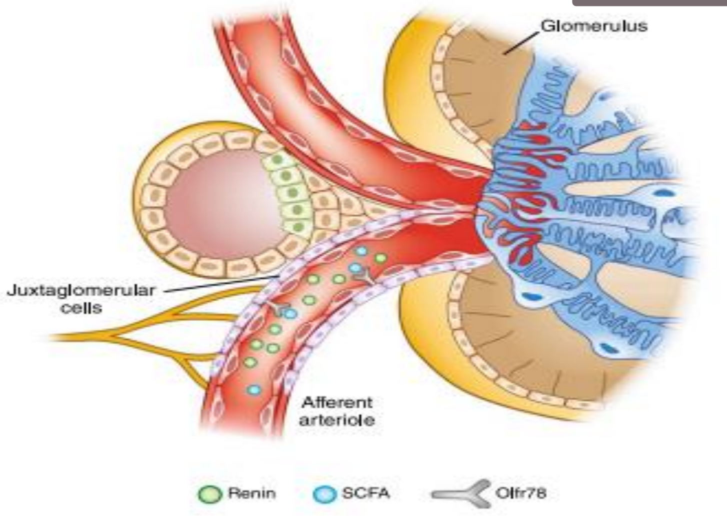


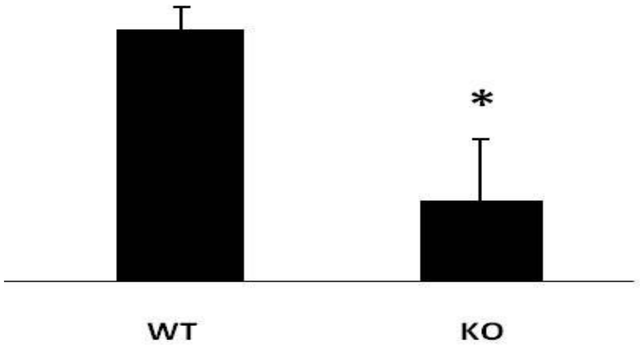
Data collected in collaboration with Dr. Peti-Peterdi, USC.; PNAS 2013

Effect of Propionate on Renin Release in WT and 78KO mice

Olfr78 KO mice also have *decreased* plasma renin

(PNAS 2013)



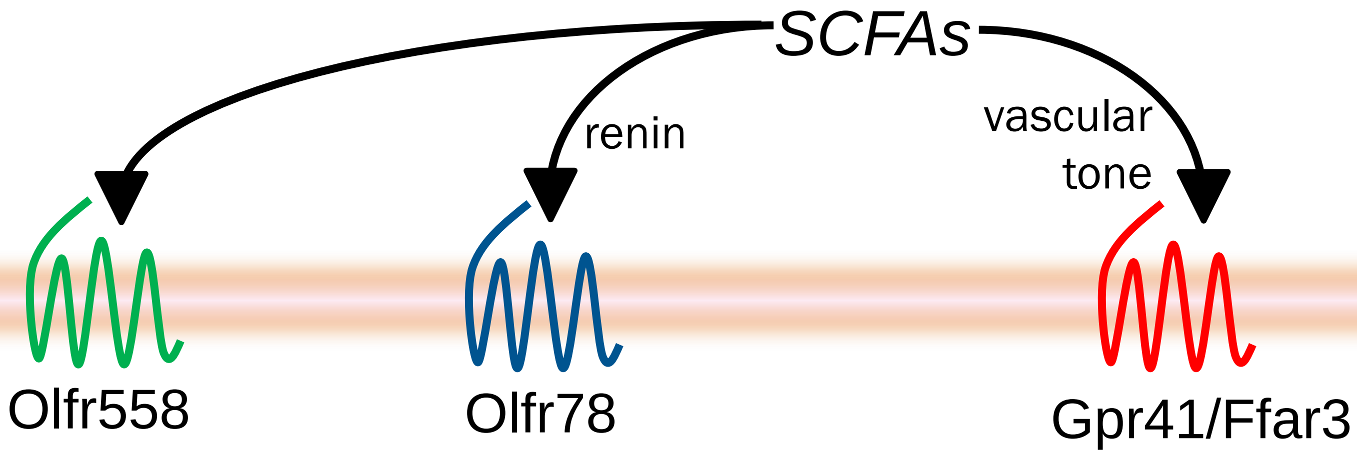


10mM propionate added to bath

Data collected in collaboration with Dr. Peti-Peterdi, USC.; PNAS 2013

Summary

SCFA receptors play roles to couple changes in microbial metabolites to changes in blood pressure regulation.



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NIH National Institute of Diabetes and Digestive and Kidney Diseases

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