Sensory Perception


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Introduction

Reactome is an open-source, open-access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references


Reactome database release: 78

This document contains 5 pathways (see Table of Contents)
Sensory perception includes the reactions and physical events that are required to receive a stimulus, convert the stimulus to a molecular signal, and sense the signal. This module includes pathways describing the sensory perception of light (visual transduction, reviewed in Grossniklaus et al. 2015, Molday and Moritz 2015, Lankford et al. 2020), volatile chemicals (olfaction, reviewed in Glezer and Malnic 2019, Lankford et al. 2020), tastants (chemicals that activate taste receptors, reviewed in Roper and Chaudhari et al. 2017), and sound (reviewed in Fettiplace 2017).

**Literature references**


**Editions**

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Mammalian Olfactory Receptor (OR, also called odorant receptor) genes were discovered in rats by Linda Buck and Richard Axel, who predicted that odorants would be detected by a large family of G protein-coupled receptors (GPCRs) that are selectively expressed in the olfactory epithelium. This prediction was based on previous biochemical evidence that cAMP levels increased in olfactory neurons upon odor stimulation. These predictions proved to be accurate, and Buck and Axel received a Nobel Prize for this and subsequent work (reviewed in Keller & Vosshall 2008).

Subsequent work in mice and other vertebrates has confirmed that OR genes are comprised of a very large family of G Protein-Coupled Receptors (GPCRs) that are selectively-expressed in olfactory epithelium. Although some OR are also expressed selectively in one or a few other tissues, their expression in olfactory epithelium generally indicates a functional role in mediating olfaction, where they couple binding by odorant ligands with intracellular olfactory signaling. (Note: the other subclasses of GPCR signaling pathways are described under "GPCR Signaling").

The ligands for ORs are diverse, ranging from chemical compounds to peptides. Intracellular signaling by OR proteins in mice and other mammalian systems is known to be mediated via direct interactions of OR proteins with an olfactory-specific heterotrimeric G Protein, that contains an olfactory-specific G alpha protein: G alpha S OLPH (also named "GNAL").

In model genetic systems such as mice, many candidate OR genes have been shown experimentally to function in olfactory signaling (reviewed in (Keller & Vosshall 2008). For the human OR genes, experimental analysis has been more limited, although some specific OR genes, such as OR7D4 and OR11H7P
have been confirmed to mediate olfactory response and signaling in humans for specific chemical odorants (Keller et al. 2007, Abbafy 2007). Mice and other rodents are believed to have about 1000 functional OR genes, as well as many additional pseudogenes. Based on sequence similarities, there are 960 human OR genes, but approximately half of these are pseudogenes (Keller 2008). In mice, essentially all olfactory signaling requires G-alpha-S (OLF); mouse G-OLF knockouts have been shown to lack olfactory responses (Belluscio 1998). Bona fide human OR genes identified by sequence similarity (not pseudogenes with function-blocking mutations) that are expressed in olfactory epithelium are expected to interact with G alpha S OLF containing G Protein trimers.

Of the 960 human OR genes and pseudogenes, there is experimental evidence that indicates over 430 are expressed in human olfactory epithelium, including 80 expressed OR pseudogenes (Zhang 2007).

When expressed in model cell systems mammalian olfactory receptors (ORs) are typically retained in the ER and degraded by the proteasome (McClintock et al. 1997). A study using Caenorhabditis elegans showed that the transport of ORs to the cilia of olfactory neurons required the expression and association of ORs with a transmembrane protein, ODR4 (Dwyer et al. 1998). Co-transfection of rat ORs with ODR4 enhanced the transport and expression of ORs at the cell-surface (Gimelbrant et al. 2001). These studies suggested that olfactory neurons might have a selective molecular machinery that promotes expression of ORs at the cells surface. Two human protein families have been identified as potential accessory proteins involved in the trafficking of ORs to the plasma membrane (Saito et al. 2004). Receptor transporting proteins 1 and 2 (RTP1, RTP2) both strongly induced expression of several ORs at the cell-surface. To a lesser extent, the receptor expression enhancing protein 1 (REEP1) also promoted cell-surface expression. These proteins are specifically expressed in olfactory neurons with no expression in testis, where a subset of ORs are expressed (Parmentier et al. 1992, Spehr et al. 2003). Other members of the RTP and REEP families have a widespread distribution. RTP3 and RTP4 have been shown to promote cell-surface expression of the bitter taste receptors, TAS2Rs (Behrens et al. 2006). REEP1 and REEP5 (also known as DP1) are involved in shaping the ER by linking microtubule fibers to the ER (Park et al. 2010, Voeltz et al. 2006). A recent study looking at the role of REEP in the trafficking of Alpha2A- and Alpha2C-adrenergic receptors showed that REEP1-2 and 6 enhance the cell-surface expression of Alpha2C, but not Alpha2A, by increasing the capacity of ER cargo, thereby allowing more receptors to reach the cell-surface (Bjork et al. 2013). Unlike RTP1, REEP1-2 and 6 are only present in the ER, do not traffic to the plasma membrane and specifically interact with the minimal/non-glycosylated forms of Alpha2C via an interaction with its C-terminus (Saito et al. 2004, Bjork et al. 2013). REEPs may function as general modulators of the ER, rather than specifically interacting with GPCRs. Loss of association of REEP2 with membranes leads to hereditary spastic paraplegia (Esteves et al. 2014).

Olfactory receptors (ORs, also called odorant receptors) are present on the plasma membrane of cilia of olfactory sensory neurons located in the olfactory epithelium of the nasal sinus. Each mature neuron expresses only one OR gene (reviewed in Nagai et al. 2016) and each OR binds one particular volatile chemical or set of volatile chemicals, known as odorants. The binding of an odorant to an OR (Mainland et al. 2015) causes a conformational change in the receptor that activates the G alpha subunit (Golf, GNAL) of an associated heterotrimeric G protein complex to exchange GDP for GTP (inferred from mouse homologs in Jones et al. 1990). GNAL:GTP and the Gbeta:Ggamma subcomplex (GNB1:GNG13) dissociate from the olfactory receptor and GNAL:GTP then binds and activates adenylyl cyclase 3 (ADCY3) (inferred from rat homologs in Bakalyar and Reed 1990, reviewed in Boccaccio et al. 2021). Cyclic AMP produced by ADCY3 binds and opens the olfactory cyclic nucleotide-gated channel (CNG channel) composed of CNGA2, CNGA4, and CNGB isoform 1b (inferred from rat homologs in Liman and Buck 1994). The CNG channel translocates sodium and calcium cations from the extracellular region into the cytosol. The resulting cytosolic calcium ions bind ANO2 and increase the transport of chloride ions by ANO2 from the cytosol to the extracellular region (inferred from mouse homologs in Pifferi et al. 2009, Stephan et al.
The translocations of ions across the plasma membrane causes depolarization of the neuron yielding a receptor potential and action potential that is transmitted to the olfactory bulb of the brain.

**Literature references**


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Visual phototransduction is the process by which photon absorption by visual pigment molecules in photoreceptor cells is converted to an electrical cellular response. The events in this process are photochemical, biochemical and electrophysiological and are highly conserved across many species. This process occurs in two types of photoreceptors in the retina, rods and cones. Each type consists of two parts, the outer segment which detects a photon signal and the inner segment which contains the necessary machinery for cell metabolism. Each type of cell functions differently. Rods are very light sensitive but their flash response is slow so they work best in twilight conditions but are not good at detecting objects moving quickly. Cones are less light-sensitive and have a fast flash response so they work best in daylight conditions and are better at detecting fast moving objects than rods.

The visual pigment consists of a chromophore (11-cis-retinal, 11cRAL, A1) covalently attached to a GPCR opsin family member. The linkage is via a Schiff base forming retinylidene protein. Upon photon absorption, 11cRAL isomerises to all-trans retinal (atRAL), changing the conformation of opsin to an activated form which can activate the regulatory G protein transducin (Gt). The alpha subunit of Gt activates phosphodiesterase which hydrolyses cGMP to 5'-GMP. As high level of cGMP keep cGMP-gated sodium channels open, the lowering of cGMP levels closes these channels which causes hyperpolarization of the cell and subsequently, closure of voltage-gated calcium channels. As calcium levels drop, the level of the neurotransmitter glutamate also drops causing depolarization of the cell. This effectively relays the light signal to postsynaptic neurons as electrical signal (Burns & Pugh 2010, Korenbrot 2012, Pugh & Lamb 1993).

11cRAL cannot be synthesised in vertebrates. Vitamin A from many dietary sources is the precursor for 11cRAL. It is taken from food in the form of esters such as retinyl acetate or palmitate or one of four carotenoids (alpha-carotene, beta-carotene, gamma-carotene and beta-cryptoxanthin). Retinoids are transported from the gut to be stored in liver, until required by target organs such as the eye (Harrison & Hussain 2001, Harrison 2005). In the eye, in the form 11cRAL, it is used in the retinoid (visual) cycle to initiate phototransduction and for visual pigment regeneration to ready the photoreceptor for the next phototransduction event (von Lintig 2012, Blomhoff & Blomhoff 2006, von Lintig et al. 2010, D'Ambrosio et al. 2011, Wang & Kefalov 2011, Kefalov 2012, Wolf 2004).
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2012-04-09 Authored, Edited Jassal, B.
In mammals, sounds are processed in the cochlea, a spiral-shaped organ in the inner ear (reviewed in Basch et al. 2016, Fettiplace 2017, Koppl and Manley 2019). Low frequency sounds are sensed at the distal end (apex) of the cochlea; high frequency sounds are sensed at the proximal end (base) of the cochlea (reviewed in Dallos 1992, Manley 2018). Sound vibrations are transmitted from the eardrum through the three bones of the inner ear (malleus, incus, stapes) and the oval window of the cochlea to the fluids within the cochlea. Within the organ of Corti in the cochlea there are 3 rows of outer hair cells (OHCs) on the external side of the tunnel of Corti and 1 row of inner hair cells (IHCs) on the internal side (Spoendlin 1967). Each IHC synapses with approximately 20 afferent myelinated type I spiral ganglion neurons and functions as a sensory receptor to convert the energy of sound waves to secretion of glutamate neurotransmitter. Multiple OHCs synapse with each unmyelinated type II afferent neuron and OHCs are also synapsed with efferent medial olivocochlear fibers (Spoendlin 1967). The primary function of OHCs, however, is amplification of organ of Corti motions in response to sound (Ryan and Dallos 1975). Amplification is produced by changes in receptor-potential driven cell length caused by changes in the conformation of the unusual membrane protein prestin (SLC26A5, Zheng et al. 2000).

IHCs and OHCs sense the sonic vibrations by deflection of stereocilia on their apical surfaces (reviewed in Fettiplace et al. 2017, McPherson 2018). The stereocilia are arranged in rows of increasing height, with a stereocilium of one row connected to a stereocilium of another row by a tip link composed of a CDH23 dimer on the taller stereocilium joined at its N-termini to the N-termini of a PCDH15 dimer on the shorter stereocilium. CDH23 is connected to the cytoskeleton of the taller stereocilium via MYO7A (MyoVIIa), USH1C (Harmonin), and USH1G (Sans) (reviewed in Peng et al. 2011, Cosgrove and Zallocchi 2014, Barr-Gillespie 2015, Fettiplace 2017, McGrath et al. 2017, Cunningham and Müller 2019, Ó Maoiléidigh and Ricci 2019, Velez-Ortega and Frolenkov 2019) while PCDH15 on the shorter stereocilium interacts with LHFPL5, an auxiliary subunit of the mechanoelectrical transduction channel (MET channel, also known as the mechanotransduction channel), which contains at least TMC1 or TMC2, TMIE, and the auxiliary subunits LHFPL5 and CIB2 (reviewed in Fettiplace 2016, Qiu and Müller 2018, Corey et al. 2019). Deflec-
Depolarization of stereocilia in the direction that increases tension on the tip link causes depolarization of the cell by increasing the open probability of the MET channel, which then transports calcium and potassium into the hair cell according to the gradient of those ions between the scala media (containing endolymph at 154 mM K+ and <1 mM Ca2+) at the apex of the cell and the scala tympani (containing perilymph at 7 mM K+) at the base (reviewed in Fettiplace and Kim 2014). Similarly, compression of the tip link by deflection of the stereocilia in the opposite direction decreases the open probability of the MET channel and causes hyperpolarization of the cell.

Depolarization of IHCs causes opening of voltage-gated calcium channels arrayed in stripes on the basolateral membrane close to ribbon synapses formed between the IHC and the afferent fiber of a myelinated type I spiral ganglion neuron. This results in a localized increase in cytosolic calcium ions which interact with Otoferlin (OTOF) on glutamate-containing synaptic vesicles at the ribbon structure to activate exocytosis of glutamate into the synapse formed with the afferent neuron (reviewed in Wichmann 2015, Pangrsic and Vogl 2018). Ribbon synapses are distinguished by electron-dense ribbon structures projecting from the presynaptic membrane into the cytosol and comprising at least BASSOON, RIBEYE (an isoform of CTBP2), and PICCOLINO (an isoform of PICCOLO). The ribbon structures appear to transiently bind synaptic vesicles and facilitate resupply of synaptic vesicles at active zones to refill the pool of readily releasable vesicles (reviewed in Moser et al. 2006, Moser et al. 2020).

In contrast with IHCs, OHCs mainly function in sound amplification by decreasing up to about 4% in length in response to depolarization caused by opening of the MET channel and increasing in length in response to hyperpolarization caused by channel closing, resulting in alternating compression and decompression between the reticular lamina and the basilar membrane. The changes in the length of the OHC are caused by very rapid (microseconds), voltage-sensitive changes in the conformation of the membrane protein prestin (SLC26A5). Stereociliary ATP2B2 (PMCA2) extrudes calcium ions and basally located KCNQ4 extrudes potassium ions to repolarize the OHC.

OHCs are synapsed with efferent cholinergic medial olivocochlear fibers (reviewed in Fritzsch and Elliott 2017, Fuchs and Lauer 2019). Acetylcholine released at the synapse binds an unusual, nicotine-antagonized, nicotinic receptor comprising CHRNA9 and CHRNA10. Upon binding acetylcholine, CHRNA9:CHRNA10 transports calcium ions into the OHC. The calcium activates SK2 potassium channels (KCNN2) and BK potassium channels (KCNMA1:KCNMB1) which extrude potassium ions, hyperpolarize the OHC, and inhibit activation of the OHC.

Loud sounds can cause a temporary threshold shift (temporary loss of hearing) caused by damage to stereocilia and synapses or permanent threshold shift (permanent loss of hearing) caused by damage or death of hair cells and neurons (reviewed in Kurabi et al. 2017).

**Literature references**


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Taste buds contain at least 3 types of cells: type I cells appear to have a support (glial-like) function; type II cells are responsible for tasting sweet compounds, bitter compounds, and umami (savoury, amino acid) compounds; and type III cells are responsible for tasting sour (acidic) compounds (reviewed in Liman et al. 2014, Roper and Chaudhari 2017, Kinnamon and Finger 2019, Taruno et al. 2021). Recently identified sodium sensing cells expressing the epithelial sodium channel (ENaC) and POU2F3 are thought to be responsible for tasting low concentrations of salt and may be a subset of type II cells or a novel type of taste cell (Chandrashekar et al. 2010, reviewed in Taruno et al. 2021). High concentrations of salt appear to be detected by both type II and type III cells.

Receptors for sweet compounds, bitter compounds, and umami compounds contain an intracellular domain, transmembrane domains, and an extracellular domain that binds the ligand. The extracellular domains of receptors for sweet and umami ligands have a distinctive "venus flytrap"-shaped domain. Upon binding ligand, sweet taste receptors (TAS1R2:TAS1R3 heterodimers), bitter taste receptors (TAS2R class receptors), and umami receptors (TAS1R1:TAS1R3 heterodimers) then signal through a common downstream pathway: the receptor-ligand complex activates an associated heterotrimeric G protein complex (GNAT3:GNB1 or GNB3:GNG13) to exchange GDP for GTP, the heterotrimeric G protein complex dissociates and the resulting GNB1,3:GNG13 complex activates Phospholipase C beta-2 (PLCB2) which hydrolyzes phosphoinositol 4,5-bisphosphate (PI(4,5)P2) to yield inositol 1,4,5-trisphosphate (I(1,4,5)P3) and diacylglycerol (DAG). I(1,4,5)P3 binds and activates ITPR3 to release calcium ions from the endoplasmic reticulum into the cytosol. Cytosolic Ca2+ causes TRPM5 sodium channels to open and depolarize the cell. SCN2A, SCN3A, and SCN9A sodium channels also appear to augment the depolarization. Depolarization causes opening of CALHM1:CALHM3 channels which transport ATP from the cytosol to the extracellular region. ATP then acts as a neurotransmitter in the taste sensing system.

Alternative pathways exist for sensing sugars and glutamate, as evidenced by residual signaling activity in the absence of TAS1R1 or TAS1R3. Glutamate is sensed by the glutamate receptors GRM1 (mGluR1)
and GRM4 (mGluR4) expressed in type II taste cells. GRM1 and GRM4 activate calcium channels by an incompletely characterized mechanism that probably involves heterotrimeric G proteins. Glucose may be sensed by a pathway comprising transport into type II taste cells via the glucose transporters SGLT1 and GLUT4, generation of ATP, and inhibition of KATP potassium channels by ATP.

Protons (H+ ions) from acidic compounds translocate from the extracellular region to the cytosol of type III taste cells through the OTOP1 channel. Weak acids such as acetic acid and citric acid are also able to enter type III cells by diffusing through the membrane in their protonated, uncharged forms. Once in the cytosol, the H+ ions inhibit KCNJ2 inwardly rectifying potassium channels, depolarizing the cell. The H+ ions may also open unidentified sodium channels to further depolarize the cell. Depolarization causes exocytosis of the neurotransmitters serotonin (5-HT) and gamma-aminobutyric acid (GABA).

Low concentrations of salt appear to be sensed in specific salt-sensing cells that may be a subset of type II cells. Low concentrations of salt are believed to enter the cell through an epithelial sodium channel (ENaC, SCNN) and the ability to taste low concentrations of salt is dependent on the SCNN1A pore-containing subunit of the SCNN complex in mice. Human taste cells express both SCNN1A and SCNN1D pore-containing subunits. The composition of other subunits of the complex is less certain. The transport of sodium ions (Na+) into the cells depolarizes the plasma membrane and eventually leads to opening of CALHM1:CALHM3 channels which transport ATP from the cytosol to the extracellular region.

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