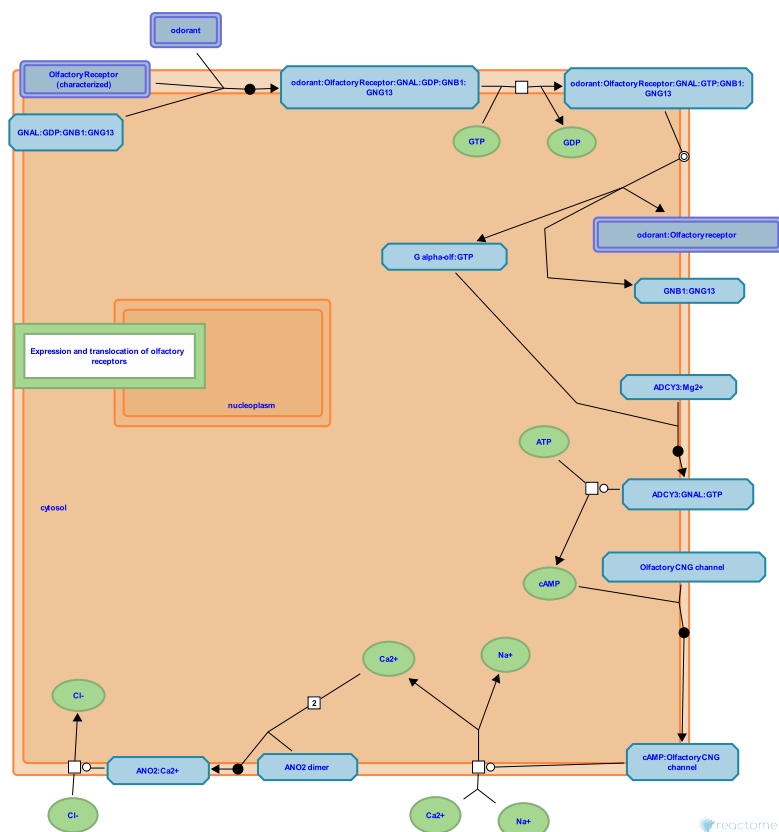


# Olfactory Signaling Pathway



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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the [Reactome Textbook](https://reactome.org/textbook/).

17/09/2024

## Introduction

Reactome is 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

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics*, 18, 142. [↗](#)

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics*, 33, 3461-3467. [↗](#)

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res*, 46, D649-D655. [↗](#)

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology*, 14, e1005968. [↗](#)

Reactome database release: 89

This document contains 2 pathways and 9 reactions ([see Table of Contents](#))



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 DPI) 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 adenylate 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. 2009). 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

- Perret, J., Schurmans, S., Mollereau, C., Ledent, C., Gerard, C., Schiffmann, S. et al. (1992). Expression of members of the putative olfactory receptor gene family in mammalian germ cells. *Nature*, 355, 453-5. [↗](#)
- Keller, A., Vosshall, L.B. (2008). Better smelling through genetics: mammalian odor perception. *Curr Opin Neurobiol*, 18, 364-9. [↗](#)
- Gilad, Y., Firestein, S., Nicolae, D., De la Cruz, O., Pinto, J.M., Zhang, X. (2007). Characterizing the expression of the human olfactory receptor gene family using a novel DNA microarray. *Genome Biol*, 8, R86. [↗](#)
- Armelin-Correa, L.M., Nagai, M.H., Malnic, B. (2016). Monogenic and Monoallelic Expression of Odorant Receptors. *Mol Pharmacol*, 90, 633-639. [↗](#)
- Oldham, W.M., Hamm, H.E. (2008). Heterotrimeric G protein activation by G-protein-coupled receptors. *Nat Rev Mol Cell Biol*, 9, 60-71. [↗](#)

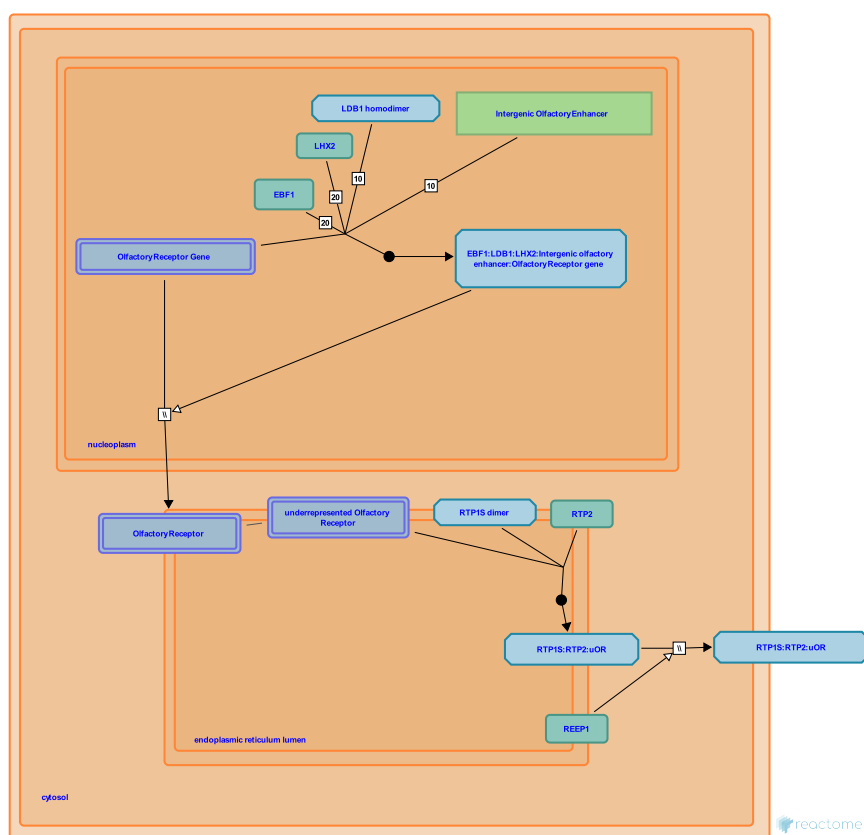
## Editions

2008-11-21	Authored	Caudy, M.
2008-12-03	Reviewed	Vosshall, L.
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## Expression and translocation of olfactory receptors ↗

**Location:** Olfactory Signaling Pathway

**Stable identifier:** R-HSA-9752946



Olfactory receptors (ORs) are 7-pass transmembrane G protein-coupled receptors (GPCRs) located on dendritic cilia of olfactory sensory neurons (OSNs) of the olfactory epithelium (reviewed in Persuy et al. 2015). ORs are also located on cells of some other tissues (reviewed in Oh 2015). ORs bind ligands, called odorants, and activate downstream signaling through a heterotrimeric G-protein leading to opening of olfactory cyclic nucleotide-gated channels (CNG channels) and depolarization of the OSN. The human genome contains about 857 OR genes of which about 394 appear to be capable of encoding a functional OR. The remaining putative OR genes appear to be pseudogenes functionally inactivated by mutations.

Each OR binds a particular odorant or family of odorants. In order to provide odor discrimination, each OSN expresses only one OR gene and connects to specific olfactory bulb glomeruli according to the specific OR expressed (reviewed in Monahan and Lomvardas 2015, McClintock et al. 2020, Sakano et al. 2020). The choice of which OR gene to express is made by an epigenetic mechanism (reviewed in Bashkirova and Lomvardas 2019). Initially during OSN development, OR genes are heterochromatic. A few OR genes become weakly expressed and one then becomes dominant while all other OR genes remain silenced by heterochromatin. During activation of an OR gene, LHX2, LDB1, and EBF1 bind several (~60) intergenic enhancers located between OR genes on 18 chromosomes. The LHX2:LDB1:EBF1:enhancer complexes assemble into an interchromosomal super-enhancer that associates with the expressed OR gene and drives transcription.

Accumulation of OR protein in the endoplasmic reticulum membrane activates the unfolded protein response (UPR) that activates translation of ADCY3, which downregulates the histone methyltransferase KDM1A (LSD1) thereby preventing activation of any other OR genes (Lyons et al. 2013, Dalton et al. 2013).

Most OR proteins are inefficiently translocated from the endoplasmic reticulum membrane to the plasma membrane when they are expressed in heterologous cells. OSNs contain specific proteins that act as chaperones to increase subcellular translocation of at least some ORs (reviewed in Mainland and Matsunami 2012). The short isoform of RTP1 (RTP1S) and RTP2 bind the OR in the endoplasmic reticulum, are translocated with the OR to the plasma membrane, and remain at the plasma membrane. REEP1 more weakly increases translocation of ORs by an uncharacterized mechanism.

## Literature references

Oh, SJ. (2018). System-Wide Expression and Function of Olfactory Receptors in Mammals. *Genomics Inform*, 16, 2-9. ↗

- Lomvardas, S., Dalton, RP., Lyons, DB. (2013). Co-opting the unfolded protein response to elicit olfactory receptor feedback. *Cell*, 155, 321-32. [↗](#)
- Sanz, G., Thomas-Danguin, T., Tromelin, A., Pajot-Augy, E., Gibrat, JF., Persuy, MA. (2015). Mammalian olfactory receptors: molecular mechanisms of odorant detection, 3D-modeling, and structure-activity relationships. *Prog Mol Biol Transl Sci*, 130, 1-36. [↗](#)
- Sakano, H. (2020). Developmental regulation of olfactory circuit formation in mice. *Dev Growth Differ*, 62, 199-213. [↗](#)
- Lomvardas, S., Monahan, K. (2015). Monoallelic expression of olfactory receptors. *Annu Rev Cell Dev Biol*, 31, 721-40. [↗](#)

## Editions

2021-08-31	Authored, Edited	May, B.
2021-11-10	Reviewed	Raimondi, F.

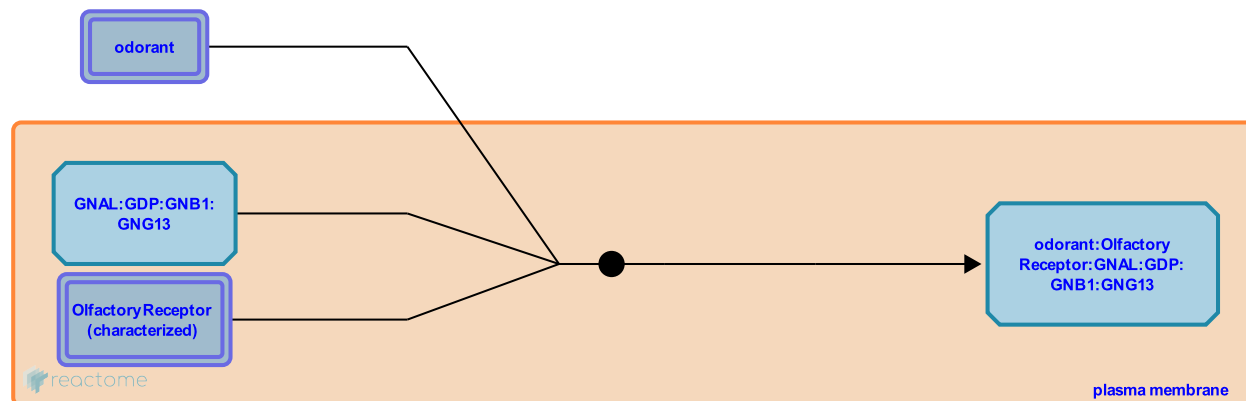
## odorant binds Odorant Receptor:GNAL:GDP:GNB1:GNGT1 ↗

**Location:** [Olfactory Signaling Pathway](#)

**Stable identifier:** R-HSA-9712210

**Type:** binding

**Compartments:** plasma membrane



Odorants, volatile chemicals, bind olfactory receptors present in the plasma membrane of cilia of olfactory sensory neurons of the main olfactory epithelium lining the nasal sinus (Wetzel et al. 1999, Keller et al. 2007, Menashe et al. 2007, Schmiedeberg et al. 2007, Cook et al. 2009, Mainland et al. 2014, Gonzalez-Kristeller et al. 2015, Mainland et al. 2015, Geithe et al. 2017, Noe et al. 2017, Sanmarti-Espinal et al. 2017, Trimmer et al. 2019). Each olfactory sensory neuron expresses one olfactory receptor gene and each olfactory receptor binds a particular set of odorants, usually members of a family of chemicals containing characteristic chemical groups such as aldehydes (Mainland et al. 2015).

**Followed by:** [GNAL exchanges GDP for GTP in odorant:Olfactory Receptor:GNAL:GDP:GNB1:GNG13](#)

## Literature references

- Li, YR., Moberly, AH., Matsunami, H., Lin, A., Adipietro, KA., Zhan, S. et al. (2014). The missense of smell: functional variability in the human odorant receptor repertoire. *Nat Neurosci*, 17, 114-20. ↗
- Li, YR., Matsunami, H., Zhou, T., Mainland, JD., Liu, WL. (2015). Human olfactory receptor responses to odorants. *Sci Data*, 2, 150002. ↗
- Geithe, C., Protze, J., Krause, G., Kreuchwig, F., Krautwurst, D. (2017). Structural determinants of a conserved enantiomer-selective carvone binding pocket in the human odorant receptor OR1A1. *Cell Mol Life Sci*, 74, 4209-4229. ↗
- Galante, PA., Gonzalez-Kristeller, DC., Malnic, B., do Nascimento, JB. (2015). Identification of agonists for a group of human odorant receptors. *Front Pharmacol*, 6, 35. ↗
- Hatt, H., Wetzel, CH., Gisselmann, G., Kuczkowiak, M., Wellerdieck, C., Oles, M. (1999). Specificity and sensitivity of a human olfactory receptor functionally expressed in human embryonic kidney 293 cells and *Xenopus Laevis* oocytes. *J Neurosci*, 19, 7426-33. ↗

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## GNAL exchanges GDP for GTP in odorant:Olfactory Receptor:GNAL:GDP:GNB1:GNG13 ↗

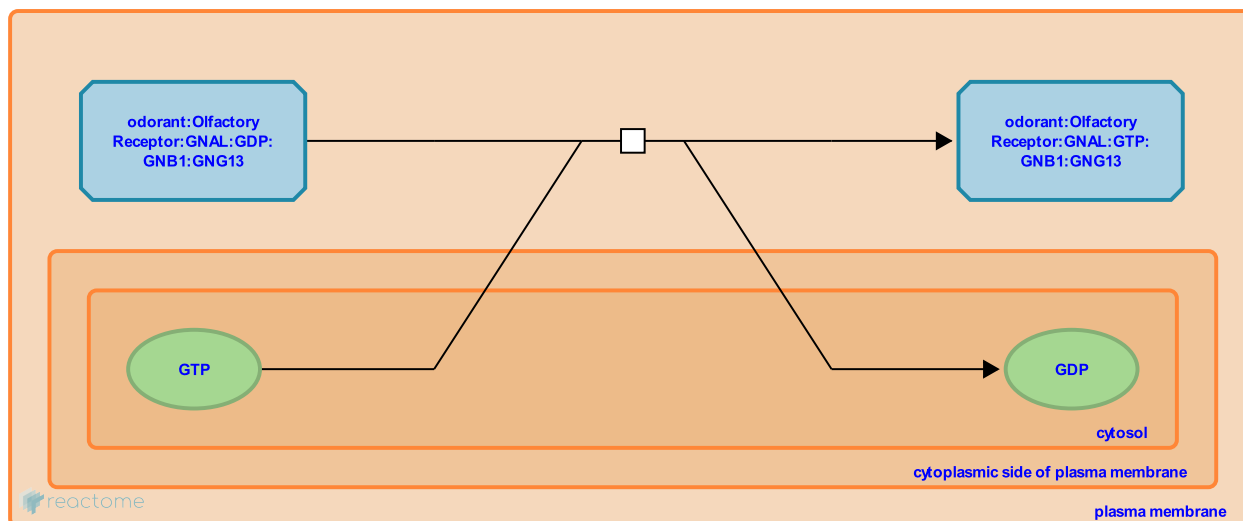
**Location:** [Olfactory Signaling Pathway](#)

**Stable identifier:** R-HSA-9712201

**Type:** transition

**Compartments:** plasma membrane

**Inferred from:** [Gnal exchanges GDP for GTP \(Rattus norvegicus\)](#)



Olfactory receptors are associated with trimeric G protein complexes containing the GNAL (Golf, G alpha olf) alpha subunit, the GNB1 beta subunit, and the GNG13 gamma subunit. The binding of an odorant to an olfactory receptor causes the GNAL subunit to exchange GDP for GTP (Borgmann-Winter et al. 2016, and inferred from rat homologs). GNAL is a member of the Gs family of G alpha proteins.

**Preceded by:** [odorant binds Odorant Receptor:GNAL:GDP:GNB1:GNGT1](#)

**Followed by:** [odorant:Olfactory Receptor:GNAL:GTP:GNB1:GNG13 dissociates yielding GNAL:GTP \(G alpha-olf:GTP\), odorant:OlfactoryReceptor, and GNB1:GNG13](#)

## Literature references

Moberg, PJ., Hahn, CG., Rawson, NE., Gur, RE., Ray, R., Wang, HY. et al. (2016). Altered G Protein Coupling in Olfactory Neuroepithelial Cells From Patients With Schizophrenia. *Schizophr Bull*, 42, 377-85. ↗

## Editions

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**odorant:Olfactory Receptor:GNAL:GTP:GNB1:GNG13 dissociates yielding GNAL:GTP (G alpha-olf:GTP), odorant:OlfactoryReceptor, and GNB1:GNG13 ↗**

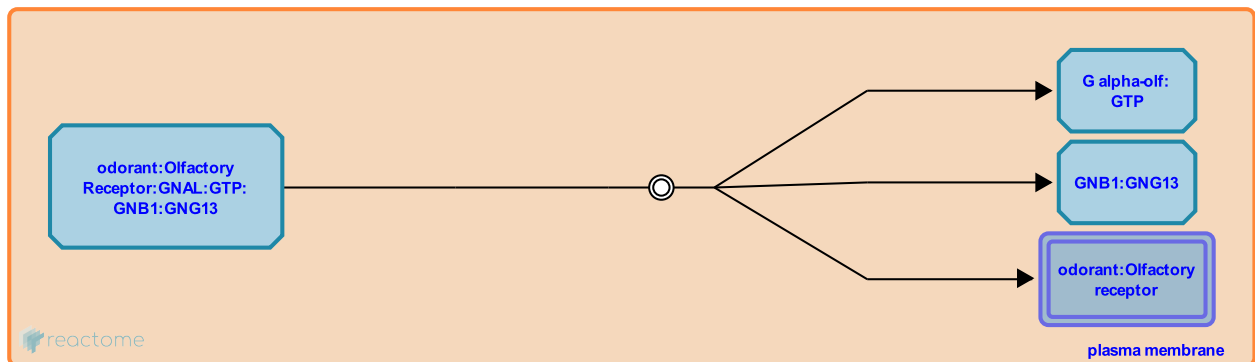
**Location:** [Olfactory Signaling Pathway](#)

**Stable identifier:** R-HSA-9712208

**Type:** dissociation

**Compartments:** plasma membrane

**Inferred from:** [The Ligand:GPCR:Gs complex dissociates \(Homo sapiens\)](#)



After GNAL binds GTP, the GNAL:GTP complex dissociates from the G beta-gamma complex (GNB1:GNG13) and the olfactory receptor (inferred from other Gs family proteins).

**Preceded by:** [GNAL exchanges GDP for GTP in odorant:Olfactory Receptor:GNAL:GDP:GNB1:GNG13](#)

**Followed by:** [GNAL:GTP \(G alpha-olf\) binds ADCY3](#)

## **Editions**

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## GNAL:GTP (G alpha-olf) binds ADCY3 ↗

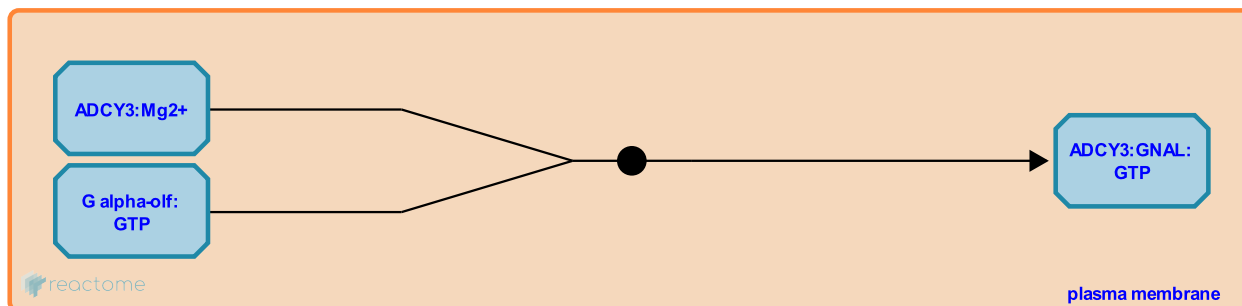
**Location:** [Olfactory Signaling Pathway](#)

**Stable identifier:** R-HSA-9712187

**Type:** binding

**Compartments:** plasma membrane

**Inferred from:** [G alpha \(s\) activates adenylate cyclase \(Homo sapiens\)](#)



The GNAL:GTP complex binds the adenylate cyclase ADCY3 bound to the cytosolic face of the plasma membrane (inferred from other G alpha (s) and ADCY family proteins).

**Preceded by:** [odorant:Olfactory Receptor:GNAL:GTP:GNB1:GNG13 dissociates yielding GNAL:GTP \(G alpha-olf:GTP\), odorant:OlfactoryReceptor, and GNB1:GNG13](#)

**Followed by:** [ADCY3:GNAL:GTP converts ATP to cAMP](#)

### Editions

2021-01-11	Authored, Edited	May, B.
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## ADCY3:GNAL:GTP converts ATP to cAMP ↗

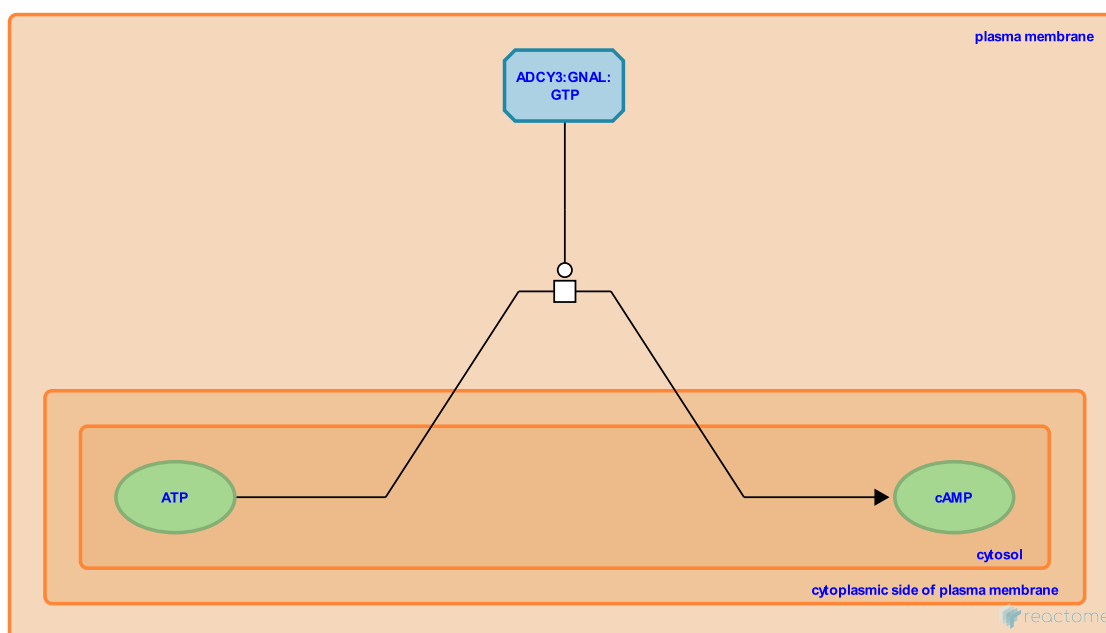
**Location:** [Olfactory Signaling Pathway](#)

**Stable identifier:** R-HSA-9712183

**Type:** transition

**Compartments:** plasma membrane

**Inferred from:** [Adcy3:Gnal:GTP converts ATP to cAMP \(Rattus norvegicus\)](#), [Adcy3:Gnal:GTP converts ATP to cAMP \(Mus musculus\)](#)



The interaction of GNAL:GTP with ADCY3 activates ADCY3 to convert ATP to cyclic AMP (cAMP) (inferred from mouse homologs and rat homologs).

**Preceded by:** [GNAL:GTP \(G alpha-olf\) binds ADCY3](#)

**Followed by:** [cAMP binds the olfactory CNG channel](#)

## Literature references

Bedner, P., Meyerhof, W., Niessen, H., Schmiedeberg, K., Raguse, J.D., Krautwurst, D. et al. (2005). Identification of specific ligands for orphan olfactory receptors. G protein-dependent agonism and antagonism of odorants. *J Biol Chem*, 280, 11807-15. ↗

## Editions

2021-01-11	Authored, Edited	May, B.
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## cAMP binds the olfactory CNG channel ↗

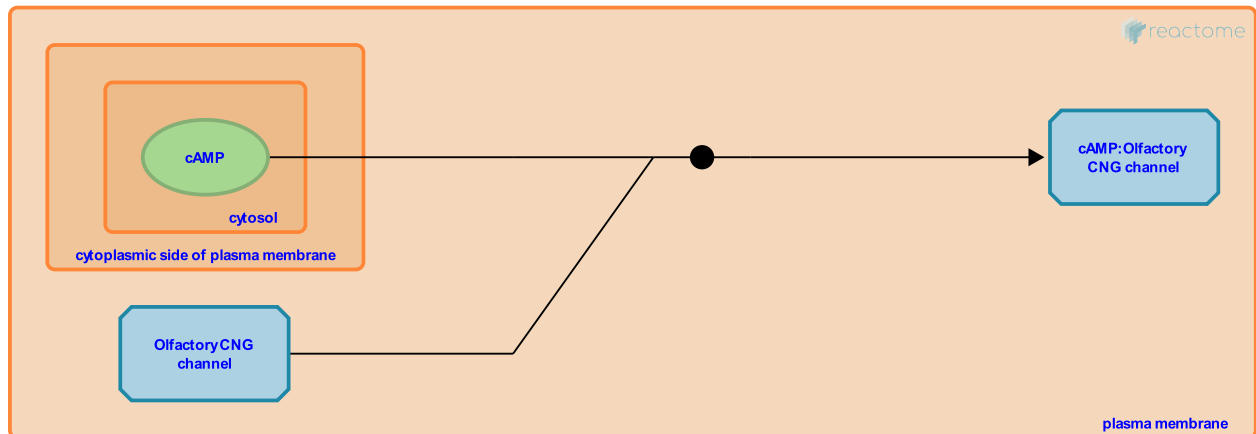
**Location:** [Olfactory Signaling Pathway](#)

**Stable identifier:** R-HSA-9712199

**Type:** binding

**Compartments:** plasma membrane

**Inferred from:** [cAMP binds the olfactory CNG channel \(Rattus norvegicus\)](#)



Cyclic AMP (cAMP) binds the cyclic nucleotide-gated channel (CNG channel) of the olfactory epithelium (inferred from rat homologs). The olfactory CNG channel contains two CNGA2 subunits, one CNGA4 subunit, and one CNGB1 subunit. Each of the subunits contains a cAMP-binding domain (inferred from rat homologs).

**Preceded by:** [ADCY3:GNAL:GTP converts ATP to cAMP](#)

**Followed by:** [cAMP:olfactory CNG channel translocates Na<sup>+</sup> and Ca<sup>2+</sup> from the extracellular region to the cytosol](#)

### Editions

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## cAMP:olfactory CNG channel translocates Na<sup>+</sup> and Ca<sup>2+</sup> from the extracellular region to the cytosol ↗

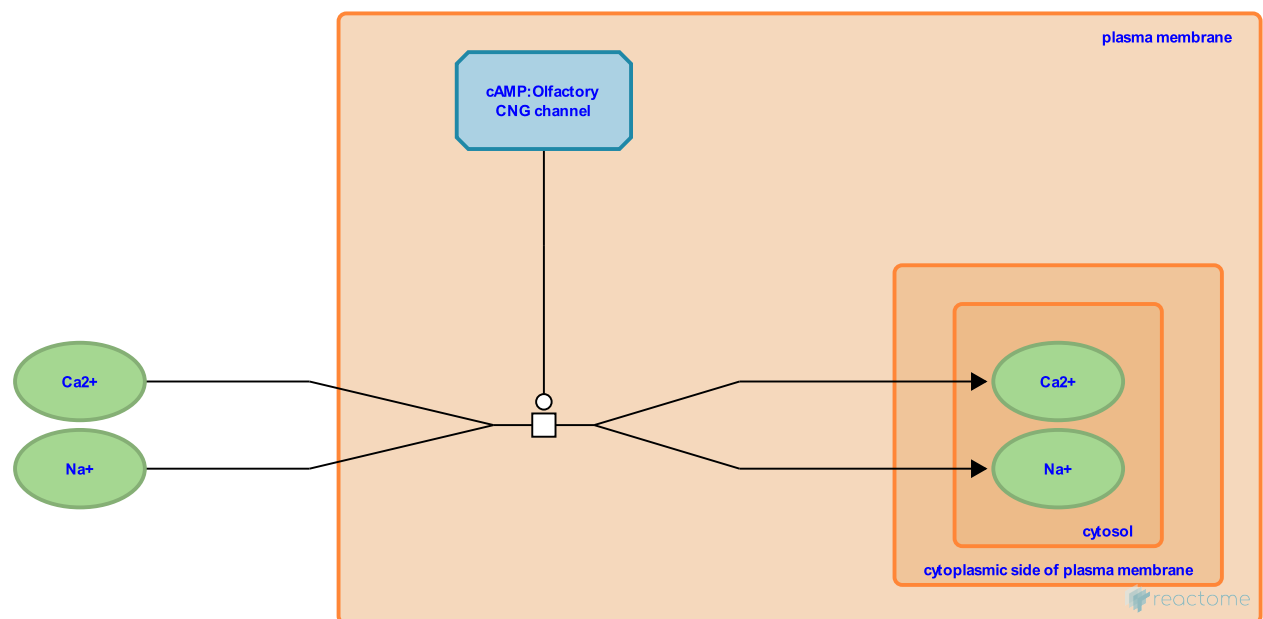
**Location:** [Olfactory Signaling Pathway](#)

**Stable identifier:** R-HSA-9712190

**Type:** transition

**Compartments:** plasma membrane

**Inferred from:** [cAMP:olfactory CNG channel translocates Na<sup>+</sup> and Ca<sup>2+</sup> from the extracellular region to the cytosol \(Mus musculus\)](#), [cAMP:olfactory CNG channel translocates Na<sup>+</sup> and Ca<sup>2+</sup> from the extracellular region to the cytosol \(Rattus norvegicus\)](#)



The olfactory cyclic nucleotide-gated channel (CNG channel) translocates sodium and calcium cations (Na<sup>+</sup>, Ca<sup>2+</sup>) from the extracellular region to the cytosol (inferred from mouse homologs and rat homologs).

**Preceded by:** [cAMP binds the olfactory CNG channel](#)

**Followed by:** [ANO2 dimer binds Ca<sup>2+</sup>](#)

### Editions

2021-01-11	Authored, Edited	May, B.
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## ANO2 dimer binds Ca2+ ↗

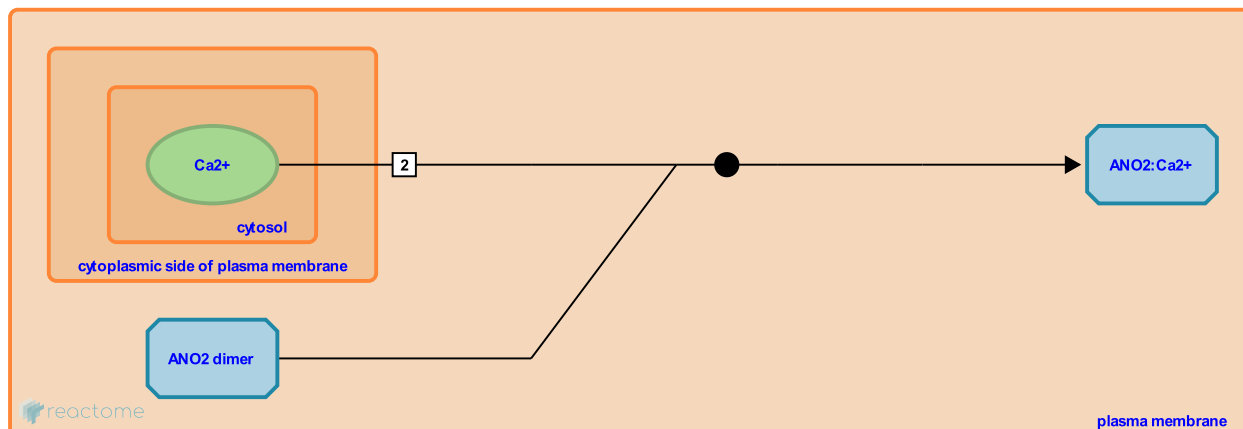
**Location:** [Olfactory Signaling Pathway](#)

**Stable identifier:** R-HSA-9712195

**Type:** binding

**Compartments:** plasma membrane

**Inferred from:** [Ano1 dimer binds Ca2+ \(Mus musculus\)](#)



Each monomer of the ANO2 dimer (TMEM16B dimer) can bind up to 2 calcium ions at locations in transmembrane helix 6-8 (inferred from mouse Ano1, Tmem16a). The first intracellular loop also plays a role in the calcium sensitivity of ANO2 but the mechanism is unknown as this site does not appear to strongly bind calcium (inferred from mouse Ano1, Tmem16a).

**Preceded by:** [cAMP:olfactory CNG channel translocates Na+ and Ca2+ from the extracellular region to the cytosol](#)

**Followed by:** [ANO2:Ca2+ translocates Cl- from the cytosol to the extracellular region](#)

## Editions

2021-01-16	Authored, Edited	May, B.
2021-08-02	Reviewed	Raimondi, F.

## ANO2:Ca<sup>2+</sup> translocates Cl<sup>-</sup> from the cytosol to the extracellular region ↗

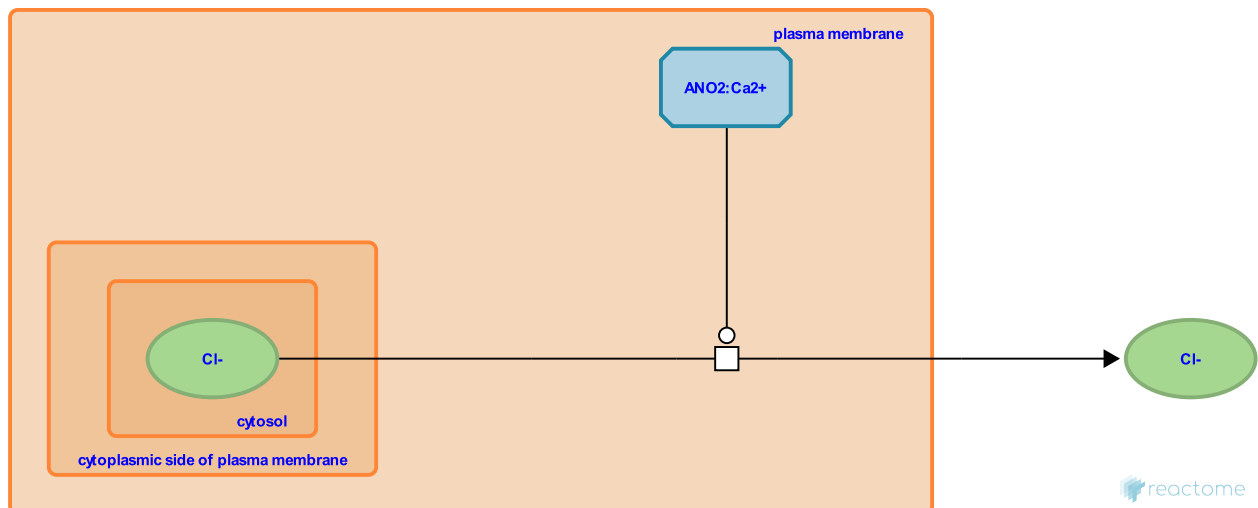
**Location:** [Olfactory Signaling Pathway](#)

**Stable identifier:** R-HSA-9712204

**Type:** transition

**Compartments:** plasma membrane

**Inferred from:** [Ano2 dimer:Ca<sup>2+</sup> translocates Cl<sup>-</sup> from the cytosol to the extracellular region \(Mus musculus\)](#)



Each monomer of the ANO2 dimer contains a pore that translocates chloride ions according to the concentration gradient from the cytosol to the extracellular region (Stöhr et al. 2009, and inferred from mouse homologs). Binding of calcium ions to sites in a transmembrane helix of each monomer increases the permeability of the pore to chloride ions.

**Preceded by:** [ANO2 dimer binds Ca<sup>2+</sup>](#)

### Literature references

Heisig, JB., Weber, BH., Wijnholds, J., Schöberl, S., Aartsen, WM., Strauss, O. et al. (2009). TMEM16B, a novel protein with calcium-dependent chloride channel activity, associates with a presynaptic protein complex in photoreceptor terminals. *J Neurosci*, 29, 6809-18. ↗

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