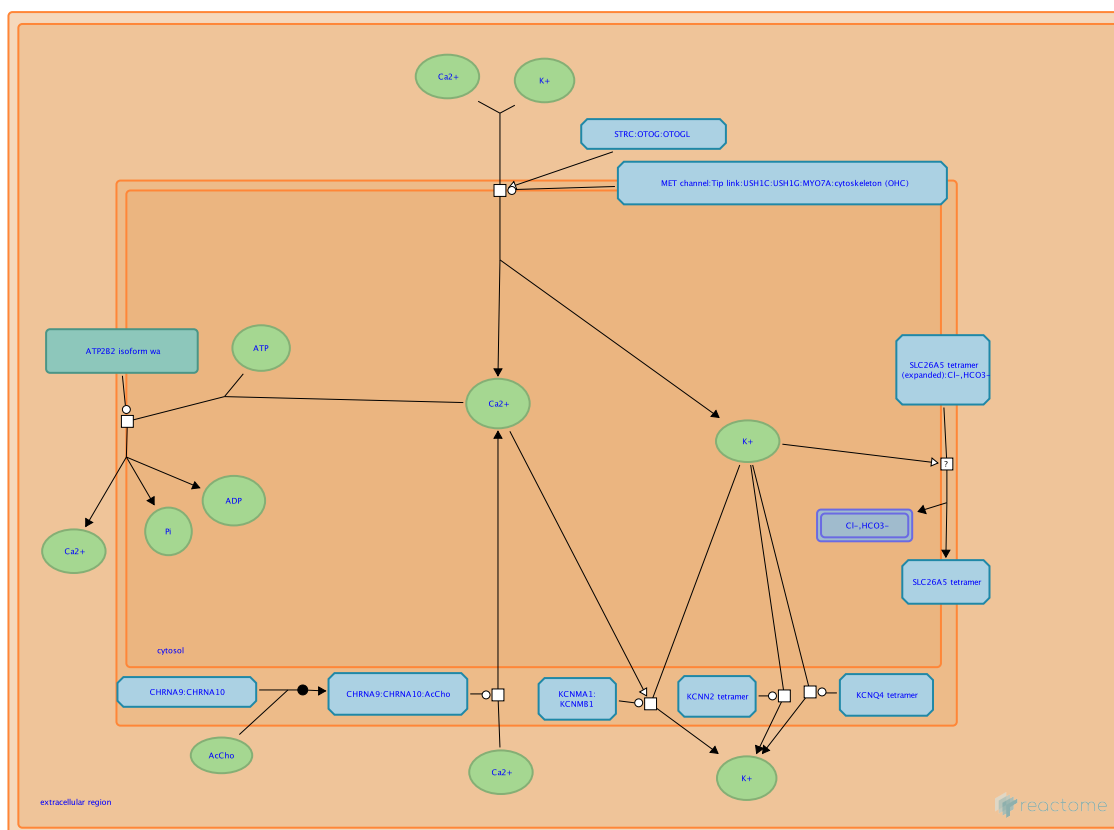


# Sensory processing of sound by outer hair cells of the cochlea



Dallos, P., Furness, DN., May, B.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of [Creative Commons Attribution 4.0 International \(CC BY 4.0\) License](https://creativecommons.org/licenses/by/4.0/). For more information see our [license](https://creativecommons.org/licenses/by/4.0/).

## 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.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

## Literature references

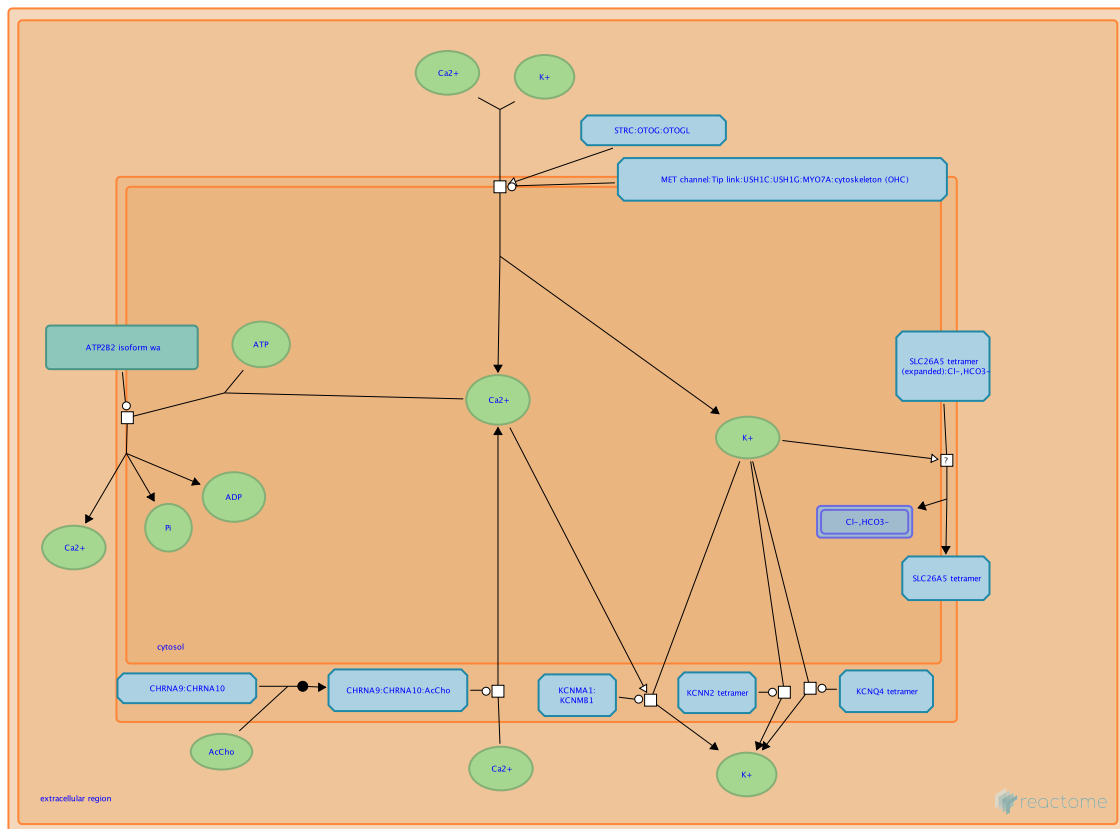
- Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics*, 18, 142. [↗](#)
- Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). 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: 77

This document contains 2 pathways and 4 reactions ([see Table of Contents](#))

## Sensory processing of sound by outer hair cells of the cochlea ↗

Stable identifier: R-HSA-9662361



Outer hair cells (OHCs) produce amplification of sound waves in the cochlea by shortening and lengthening in response to sound, a phenomenon called electromotility (reviewed in Kim and Fettiplace 2014, Fettiplace 2016, Fettiplace 2017, Fritzsche et al. 2017, Ashmore 2019). Like inner hair cells, OHCs possess apical stereocilia arranged in rows of ascending height. A taller stereocilium is connected to a shorter stereocilium by a tip link comprising a CDH23 dimer on the side of the taller stereocilium and a PCDH15 dimer on the apex of the shorter stereocilium. PCDH15 interacts with LHFPL5, a subunit of the mechano-electrical transduction channel complex (MET channel, also called the mechanotransduction channel), which contains TMC1 or TMC2, TMIE, CIB2, and LHFPL5 (reviewed in Fettiplace 2016). Deflection of the stereocilia in one direction produces tension on the tip link that increases the open probability of the MET channel, resulting in depolarization of the OHC. Deflection of the stereocilia in the opposite direction produces compression on the tip link that decreases the open probability of the MET channel, resulting in hyperpolarization of the OHC.

Sound causes micromechanical motions of the organ of Corti that result in alternating tension and compression in the tip link that produce excitatory-inhibitory cycles of MET channel openings and closings relative to the MET channel's resting open probability. This causes directionally alternating fluxes of K<sup>+</sup> and Ca<sup>2+</sup>, yielding depolarization-hyperpolarization cycles that cause conformational changes in prestin (SLC26A5). These cycles are asymmetrical, with contraction caused by depolarization dominating elongation caused by hyperpolarization due to the asymmetry of the open probability of MET channels. Stereociliary ATP2B2 (PMCA2) extrudes calcium ions and basally located KCNQ4 extrudes potassium ions to repolarize the OHC.

Depolarization of the OHC causes a decrease in length of the OHC due to a very rapid, voltage-sensitive change in conformation of the membrane protein prestin (SLC26A5), an unusual member of the anion transporter family located in the lateral membrane (Mahendrasingam et al, 2010) that appears to re-

spond to cytosolic chloride by altering its conformation in the plane of the plasma membrane (reviewed in Dallos et al. 2006, Dallos 2008, Hudspeth 2014, Reichenbach and Hudspeth 2014, Ashmore 2019, Santos-Sacchi 2019). Prestin also appears to act as a weak chloride-bicarbonate antiporter (Mistrik et al. 2012). Changes in length of the OHCs cause movement of the reticular lamina toward and away from the basilar membrane.

## Literature references

Mahendrasingam, S., Beurg, M., Fettiplace, R., Hackney, CM. (2010). The ultrastructural distribution of prestin in outer hair cells: a post-embedding immunogold investigation of low-frequency and high-frequency regions of the rat cochlea. *Eur. J. Neurosci.*, *31*, 1595-605. [↗](#)

Ashmore, J. (2019). Outer Hair Cells and Electromotility. *Cold Spring Harb Perspect Med*, *9*. [↗](#)

Dallos, P. (2008). Cochlear amplification, outer hair cells and prestin. *Curr. Opin. Neurobiol.*, *18*, 370-6. [↗](#)

Reichenbach, T., Hudspeth, AJ. (2014). The physics of hearing: fluid mechanics and the active process of the inner ear. *Rep Prog Phys*, *77*, 076601. [↗](#)

Hudspeth, AJ. (2014). Integrating the active process of hair cells with cochlear function. *Nat. Rev. Neurosci.*, *15*, 600-14. [↗](#)

## Editions

2019-09-23	Authored, Edited	May, B.
2020-09-14	Reviewed	Furness, DN., Dallos, P.

## Mechanoelectrical transduction (MET) channel transports cations into the cytosol of stereocilia of cochlear outer hair cell ↗

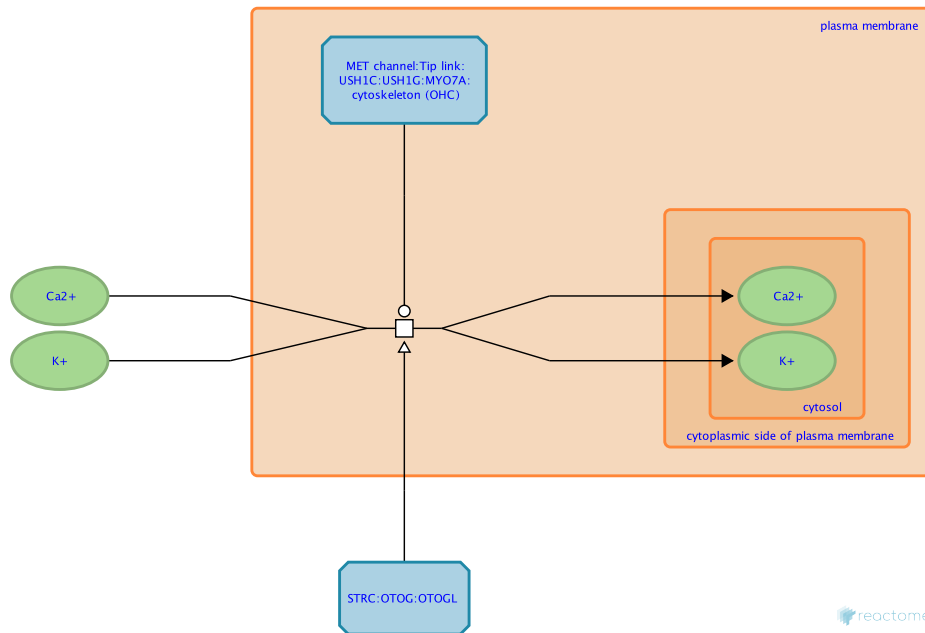
**Location:** [Sensory processing of sound by outer hair cells of the cochlea](#)

**Stable identifier:** R-HSA-9663363

**Type:** transition

**Compartments:** plasma membrane

**Inferred from:** [MET channel transports cations from the extracellular region into the cytosol of stereocilia of cochlear outer hair cell \(Mus musculus\)](#)



The mechanoelectrical transduction (MET) channels located at the tips of stereocilia on the apical surface of outer hair cells (OHCs) are opened by mechanical force exerted on the channels by CDH23:PCDH15 tip links that connect the apices of shorter stereocilia to the sides of taller stereocilia (inferred from mouse homologs). A CDH23 dimer is connected to the cytoskeleton of a taller stereocilium via USH1C (Harmonin), USH1G (SANS), and MYO7A (MYOVIIA) (inferred from mouse homologs). By a calcium-dependent interaction, a CDH23 dimer on the side of a taller stereocilium is bound to a PCDH15 dimer connected to a MET channel on the apex of a shorter stereocilium (inferred from mouse homologs). The MET channel complex contains at least TMC1 or TMC2, TMIE, CIB2, and LHFPL5, with which PCDH15 interacts (inferred from mouse homologs). Deflection of the stereocilia by sound causes increased tension on CDH23:PCDH15, resulting in an increased probability of the open state of the MET channel. The MET channel is relatively non-specific for cations and conducts calcium ions and potassium ions from the extracellular scala media into the cytosol of the OHC. Depolarization of the OHC results in shortening of the OHC due to a change in conformation of SLC26A5 (prestin) located in the lateral membrane of the OHC. The composition of the cytoskeleton of OHCs differs from that of inner hair cells (IHCs): MPP1 and GSN are present in OHCs but absent from IHCs (inferred from mouse homologs).

**Followed by:** [SLC26A5 \(prestin\) changes conformation in response to depolarization](#)

### Editions

2019-09-30

Authored, Edited

May, B.

2020-09-14

Reviewed

Furness, DN., Dallos, P.

## SLC26A5 (prestin) changes conformation in response to depolarization ↗

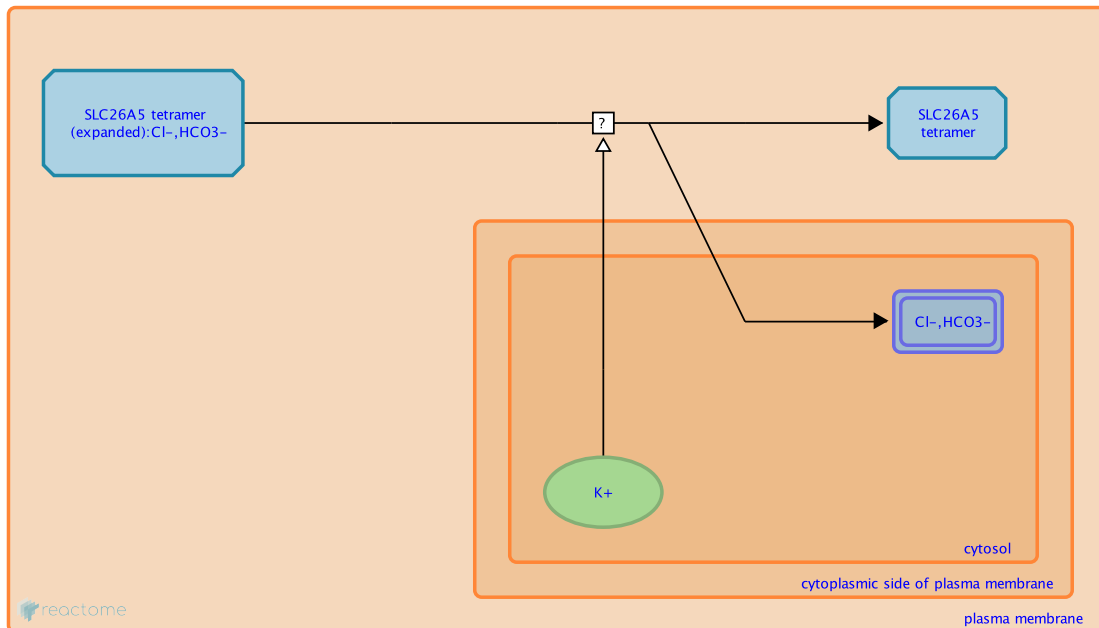
**Location:** Sensory processing of sound by outer hair cells of the cochlea

**Stable identifier:** R-HSA-9663354

**Type:** uncertain

**Compartments:** plasma membrane

**Inferred from:** [Slc26a5 changes conformation in response to depolarization \(Rattus norvegicus\)](#), [Slc26a5 changes conformation in response to depolarization \(Mus musculus\)](#)



The membrane protein SLC26A5 (prestin) contracts in the plane of the membrane in response to depolarization of the cell caused by opening of the mechanoelectric transduction (MET) channel (inferred from rat homologs). Likewise, SLC26A5 expands in the plane of the membrane in response to hyperpolarization caused by MET channel closing. A current model for the reaction posits that the association of anions (chloride or bicarbonate) with a binding pocket midway along the permeation pathway within SLC26A5 causes a change in the area occupied by SLC26A5 in the membrane (inferred from the rat homolog). An influx of cations through the MET channel causes dissociation of anions from SLC26A5, reversing the conformational change. The contraction-elongation cycle of OHCs, due to conformational changes of prestin, provides feedback-amplification of the motions (principally the reticular lamina) of the organ of Corti. At low sound levels the amplification is about a 1000-fold, decreasing nonlinearly as sound level increases. In the absence of either OHCs (Ryan and Dallos 1975) or functional prestin (inferred from mouse homologs) the amplification disappears.

**Preceded by:** [Mechanoelectrical transduction \(MET\) channel transports cations into the cytosol of stereocilia of cochlear outer hair cell](#)

### Literature references

Zheng, J., Shen, W., He, DZ., Long, KB., Madison, LD., Dallos, P. (2000). Prestin is the motor protein of cochlear outer hair cells. *Nature*, 405, 149-55. ↗

### Editions

2019-09-30

Authored, Edited

May, B.

2020-09-14

Reviewed

Furness, DN., Dallos, P.

## KCNQ4 transports K<sup>+</sup> from the cytosol to the extracellular region ↗

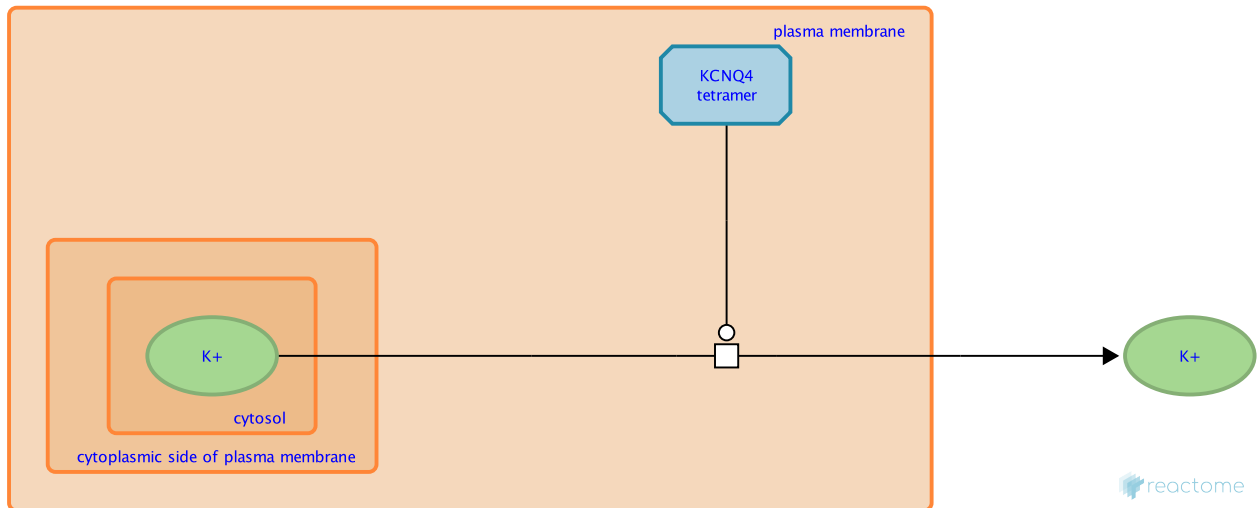
**Location:** Sensory processing of sound by outer hair cells of the cochlea

**Stable identifier:** R-HSA-9659554

**Type:** transition

**Compartments:** plasma membrane

**Inferred from:** Kcnq4 transports K<sup>+</sup> from the cytosol to the extracellular region (Mus musculus)



KCNQ4 located on the basal membrane of outer hair cells (OHCs) and the basolateral membrane of inner hair cells (inferred from the mouse homolog) transports potassium ions along the concentration gradient from the cytosol to the extracellular region (Kubisch et al. 1999 and inferred from the mouse homolog). The resulting efflux of potassium is believed to be responsible for the I(K,n) current that plays a role in setting the resting potential of the cell and in repolarization of the cell. Absence of KCNQ4 causes increased depolarization and degeneration of OHCs (inferred from the mouse homolog).

### Literature references

Kubisch, C., Schroeder, BC., Friedrich, T., Lütjohann, B., El-Amraoui, A., Marlin, S. et al. (1999). KCNQ4, a novel potassium channel expressed in sensory outer hair cells, is mutated in dominant deafness. *Cell*, 96, 437-46. ↗

### Editions

2019-08-27	Authored, Edited	May, B.
2020-09-14	Reviewed	Furness, DN., Dallos, P.

## ATP2B2-wa (PMCA2-wa) transports Ca<sup>2+</sup> from the cytosol to the extracellular region



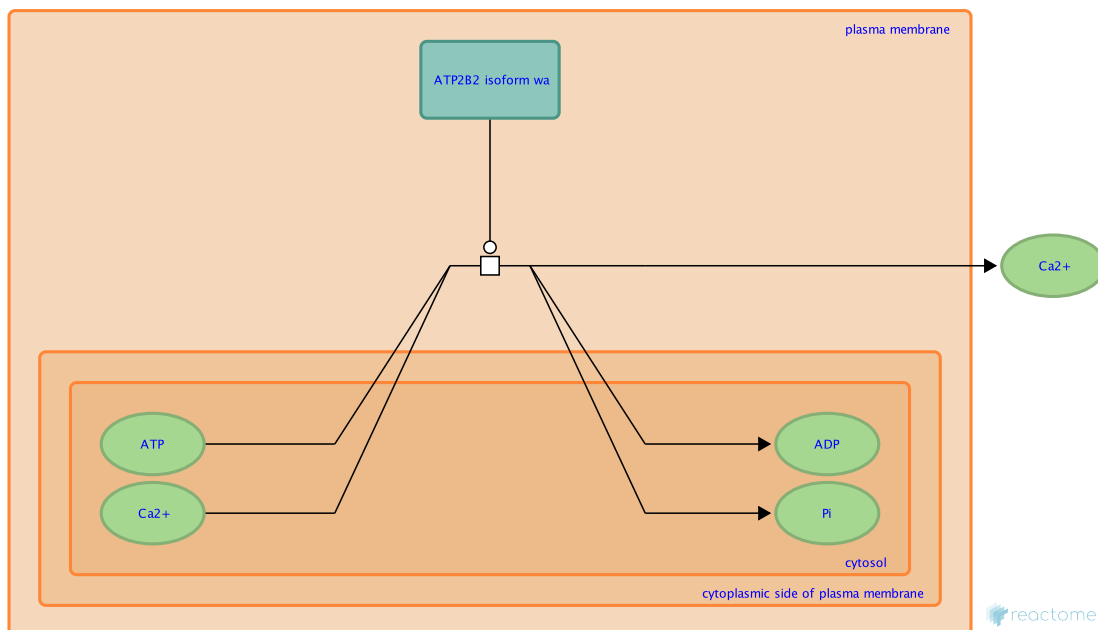
**Location:** Sensory processing of sound by outer hair cells of the cochlea

**Stable identifier:** R-HSA-9662114

**Type:** transition

**Compartments:** plasma membrane

**Inferred from:** *Atp2b2-wa* (PMCA2-wa) transports Ca<sup>2+</sup> from the cytosol to the extracellular region (*Rattus norvegicus*), *Atp2b2* (PMCA2) transports Ca<sup>2+</sup> from the cytosol to the extracellular region (*Mus musculus*)



ATP2B2 (wa isoform) is located in the plasma membrane of stereocilia bundles of inner hair cells and outer hair cells and transports calcium ions from the cytosol to the extracellular region with concomitant hydrolysis of ATP (Ficarella et al. 2007, Giacomello et al. 2011, and observed in rat and mouse). ATP2B2 appears to facilitate an efflux of calcium ions that enter the stereocilia during depolarization caused by the opening of the mechanoelectrical transduction channel, hence ATP2B2 plays a role in repolarization of the cell (Ficarella et al. 2007, Giacomello et al. 2011, and observed in rat and mouse).

### Literature references

Ficarella, R., Di Leva, F., Bortolozzi, M., Ortolano, S., Donaudy, F., Petrillo, M. et al. (2007). A functional study of plasma-membrane calcium-pump isoform 2 mutants causing digenic deafness. *Proc. Natl. Acad. Sci. U.S.A.*, 104, 1516-21. [↗](#)

Giacomello, M., De Mario, A., Lopreiato, R., Primerano, S., Campeol, M., Brini, M. et al. (2011). Mutations in PMCA2 and hereditary deafness: a molecular analysis of the pump defect. *Cell Calcium*, 50, 569-76. [↗](#)

### Editions

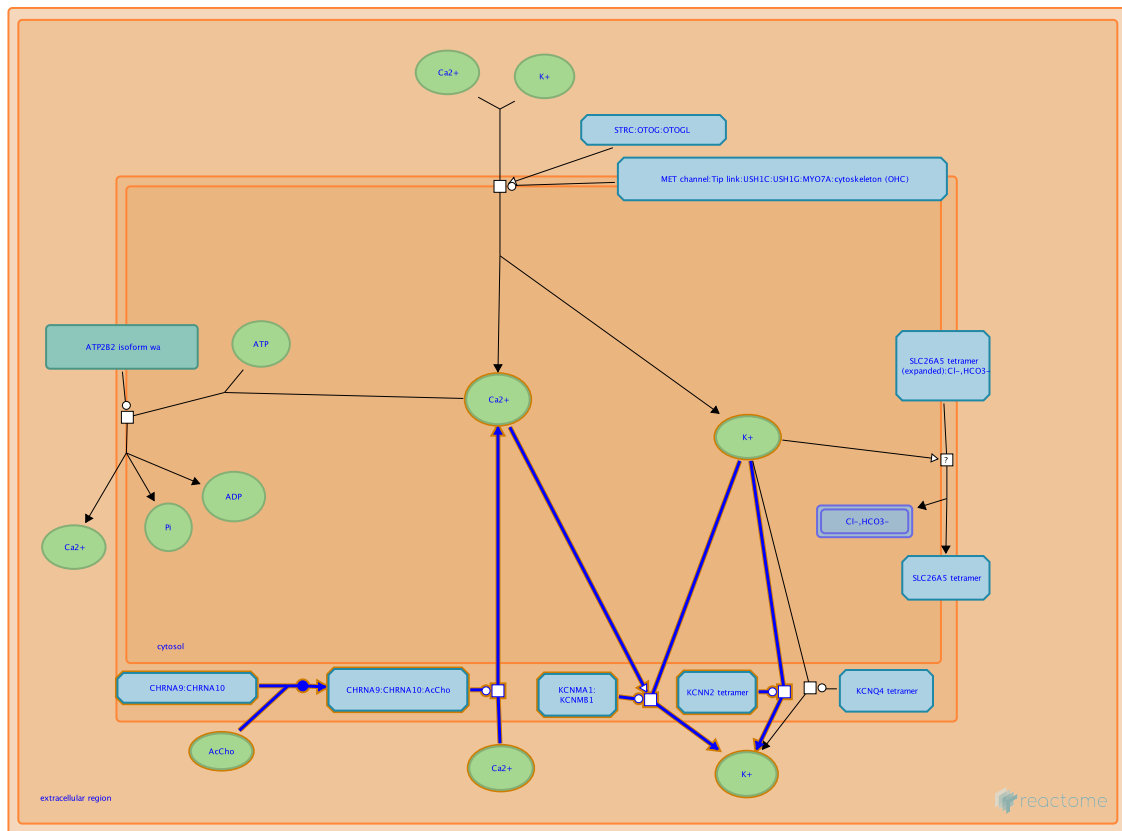
2019-09-20	Authored, Edited	May, B.
2020-09-14	Reviewed	Furness, DN., Dallos, P.



## Acetylcholine inhibits contraction of outer hair cells ↗

**Location:** Sensory processing of sound by outer hair cells of the cochlea

**Stable identifier:** R-HSA-9667769



Outer hair cells (OHCs) are synapsed with efferent cholinergic medial olivocochlear fibers (reviewed in Fritzscht 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 nearby SK2 potassium channels (KCNN2, small potassium current channels) and BK potassium channels (KCMA1:KCNMB1, big potassium current channels) which extrude potassium ions, hyperpolarize the OHC, and inhibit activation of the OHC.

The overall effects of acetylcholine on OHCs are complex. OHCs exhibit fast motility caused by voltage effect on SLC26A5 and slow motility caused by cytoskeleton organization.

### Literature references

Fritzscht, B., Elliott, KL. (2017). Evolution and Development of the Inner Ear Efferent System: Transforming a Motor Neuron Population to Connect to the Most Unusual Motor Protein via Ancient Nicotinic Receptors. *Front Cell Neurosci*, 11, 114. ↗

Fuchs, PA., Lauer, AM. (2019). Efferent Inhibition of the Cochlea. *Cold Spring Harb Perspect Med*, 9. ↗

### Editions

2019-11-16

Authored, Edited

May, B.

2020-09-14

Reviewed

Furness, DN., Dallos, P.

# Table of Contents

Introduction	1
🔊 Sensory processing of sound by outer hair cells of the cochlea	2
➤ Mechanoelectrical transduction (MET) channel transports cations into the cytosol of stereocilia of cochlear outer hair cell	4
➤ SLC26A5 (prestin) changes conformation in response to depolarization	5
➤ KCNQ4 transports K <sup>+</sup> from the cytosol to the extracellular region	6
➤ ATP2B2-wa (PMCA2-wa) transports Ca <sup>2+</sup> from the cytosol to the extracellular region	7
🔊 Acetylcholine inhibits contraction of outer hair cells	8
Table of Contents	9