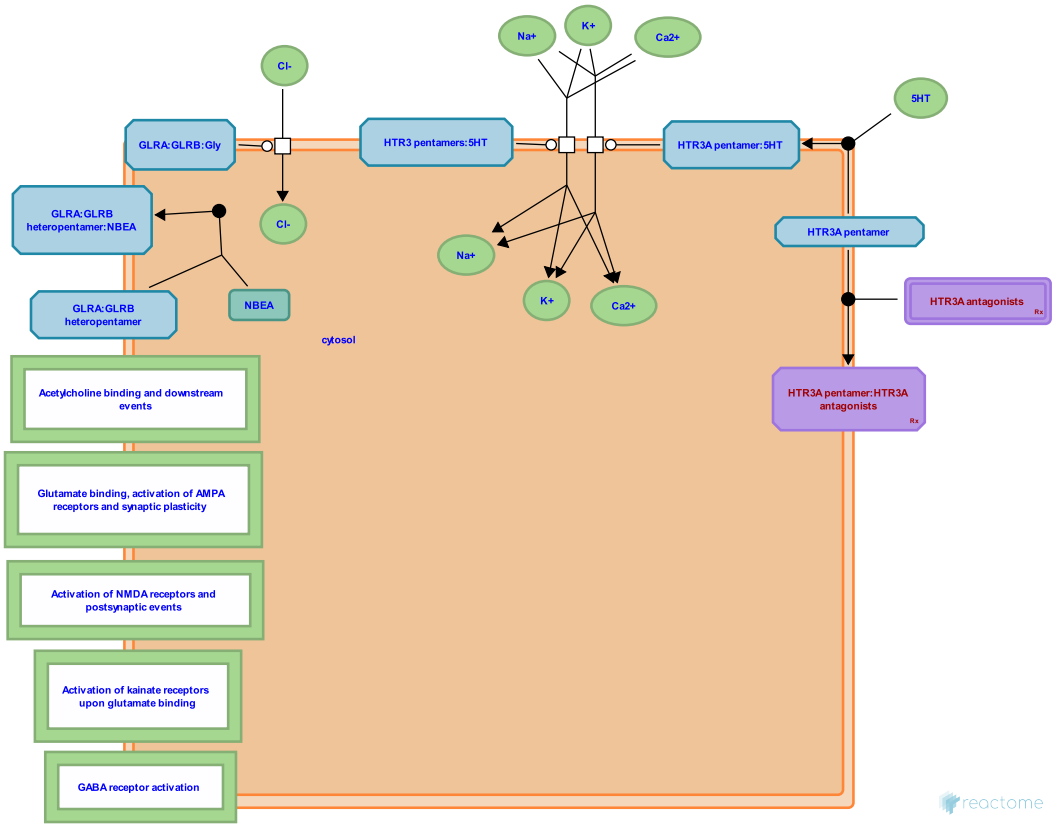
Neurotransmitter receptors and postsynaptic signal transmission



D'Eustachio, P., Gillespie, ME., Hansen, KB., He, L., Huddart, R., Jassal, B., Kavalali, E., Mahajan, SS., Martin, EA., Matthews, L., Miller, AC., Orlic-Milacic, M., Restituito, S., Tukey, D., Wen, H., Yi, F., Ziff, EB.

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

01/05/2024

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.

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. ↗

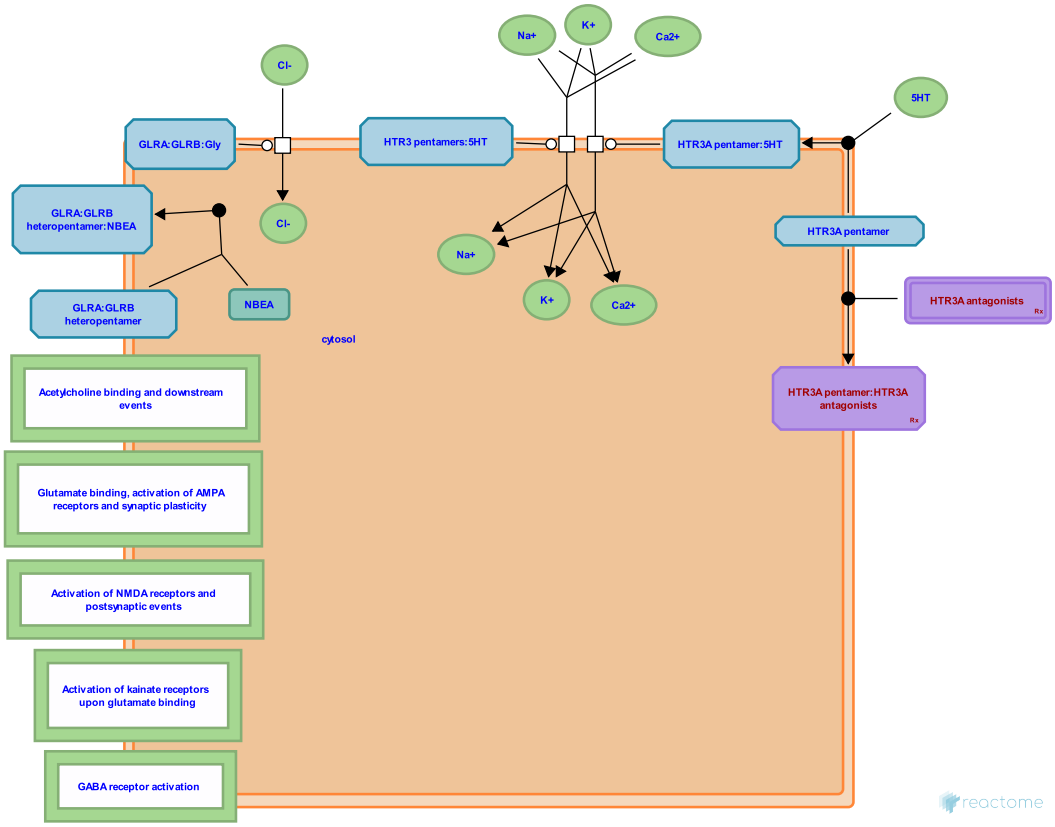
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Neurotransmitter receptors and postsynaptic signal transmission ↗

Stable identifier: R-HSA-112314



The neurotransmitter in the synaptic cleft released by the pre-synaptic neuron binds specific receptors located on the post-synaptic terminal. These receptors are either ion channels or G protein coupled receptors that function to transmit the signals from the post-synaptic membrane to the cell body.

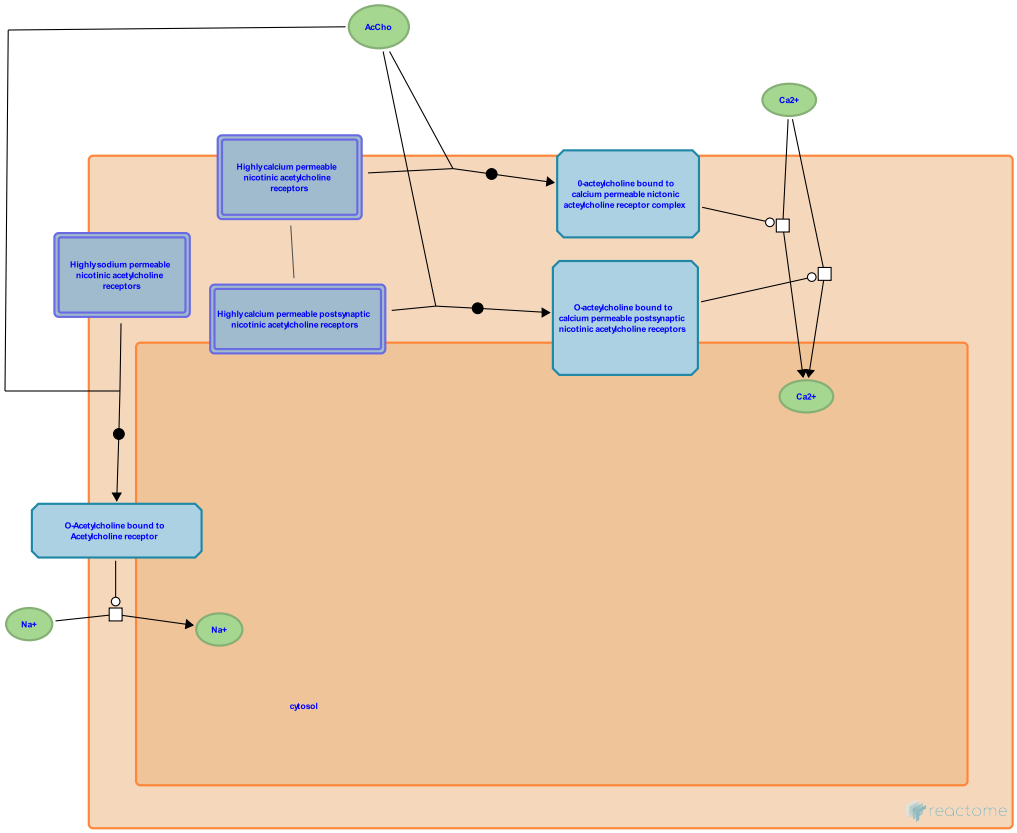
Editions

2008-01-14	Authored	Mahajan, SS.
2008-12-02	Reviewed	Kavalali, E., Restituito, S.

Acetylcholine binding and downstream events ↗

Location: Neurotransmitter receptors and postsynaptic signal transmission

Stable identifier: R-HSA-181431



Acetylcholine is the neurotransmitter found at neuromuscular junctions, synapses in the ganglia of the visceral motor system, and at a variety of sites within the central nervous system. A great deal is known about the function of cholinergic transmission at the neuromuscular junction and at ganglionic synapses, the actions of ACh in the central nervous system are not as well understood. Acetylcholine is synthesized in nerve terminals from acetyl coenzyme A (acetyl CoA) synthesized from glucose) and choline. This reaction is catalyzed by choline acetyltransferase (ChAT). The presence of acetyltransferase in a neuron is thus a strong indication that ACh is used as one of its transmitters. Choline is present in plasma at a concentration of about 10 mM, and is taken up into cholinergic neurons by a high affinity Na+/choline transporter. About 10,000 molecules of ACh are packaged into each neurotransmitter containing vesicle by a vesicular ACh transporter.
Nicotinic acetylcholine receptors (nAchR) are ionotropic receptors that can be activated by nicotine and permeable to of monovalent (sodium, potassium) and divalent cations(calcium), however, the permeability of sodium and/or calcium maybe high or low depending on the subunit composition of the receptor. Nicotinic acetylcholine receptors are expressed widely in the central and peripheral nervous system in the presynaptic terminal, terminal bouton and post synaptic neuron. Functionally nicotinic acetylcholine receptors in the pre synaptic and postsynaptic terminals behave similarly. Nicotinic AChR are a family of acetylcholine gated pentameric receptors that are formed by the association of various combinations of mostly alpha, beta subunits (for the neuronal type) and together with gamma, delta and epsilon subunits (for the muscle type). In addition, receptors may be more diverse due the fact that some receptors have same subunits but the stoichiometry of the subunits is different.

Literature references

Bertrand, D., Steinlein, OK. (2008). Neuronal nicotinic acetylcholine receptors: from the genetic analysis to neurological diseases. *Biochem Pharmacol, 76*, 1175-83. ↗

Zoli, M., Gotti, C., Manfredi, I., Guiducci, S., Clementi, F., Pucci, L. et al. (2009). Structural and functional diversity of native brain neuronal nicotinic receptors. *Biochem Pharmacol, 78*, 703-11. ↗

Pereira, EF., Alkondon, M., Albuquerque, EX., Rogers, SW. (2009). Mammalian nicotinic acetylcholine receptors: from structure to function. *Physiol Rev, 89*, 73-120. ↗

Bertrand, D., Itier, V. (2001). Neuronal nicotinic receptors: from protein structure to function. *FEBS Lett, 504*, 118-25. ↗

Editions

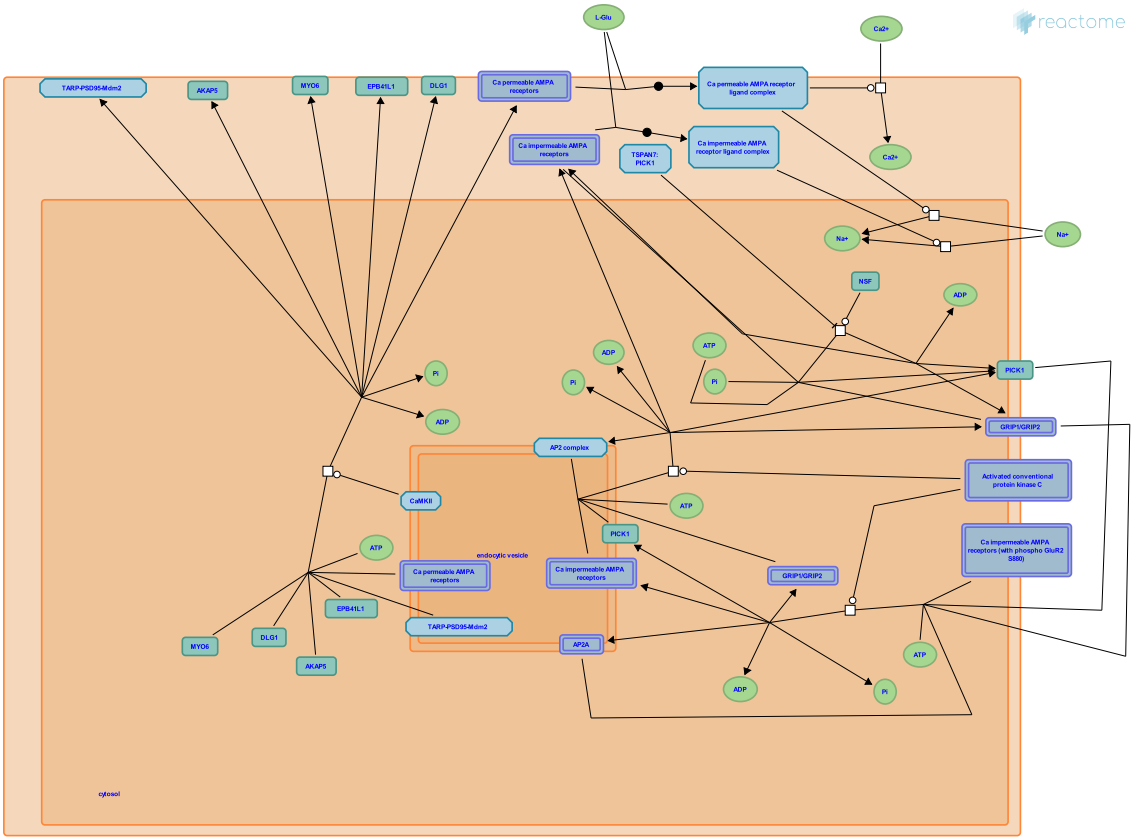
2008-01-14	Authored	Mahajan, SS.
2008-11-27	Reviewed	Restituito, S.
2020-01-24	Reviewed	Wen, H.

Glutamate binding, activation of AMPA receptors and synaptic plasticity ↗

Location: Neurotransmitter receptors and postsynaptic signal transmission

Stable identifier: R-HSA-399721

Compartments: plasma membrane, extracellular region



Excitatory synaptic transmission in the brain is carried out by glutamate receptors through the activation of both ionotropic and metabotropic receptors. Ionotropic glutamate receptors are of three subtypes based on distinct physiologic properties and their differential binding of exogenous ligands namely NMDA (N-methyl D-aspartate), AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and Kainate . The ionotropic receptors are glutamate gated ion channels that initiate signaling by influx of ions, and are comprised of subunits with distinct structures and distinguished based on their agonist binding. Even though all three types of receptors are found at the glutamatergic synapses yet they exhibit great diversity in the synaptic distribution. The metabotropic glutamate receptors are a family of G-protein coupled receptors that are slow acting. Fast excitatory synaptic transmission is carried out through AMPA receptors. Post-synaptic transmission involves binding of the ligand such as glutamate/AMPA to the AMPA receptor resulting in the Na influx which causes depolarization of the membrane. NMDA receptors are blocked by Mg at resting membrane potential. NMDA receptors are activated upon coincident depolarization and glutamate binding are activated following AMPA receptor activation.NMDA receptors are blocked by Mg at resting
membrane potential. NMDA receptors are Ca permeable and their activity leads to increase in Ca which, leads to upregulation of AMPA receptors at the synapse which causes the long lasting excitatory post-synaptic potential (EPSP) which forms the basis of long term potentiation (LTP). LTP is one form of synaptic plasticity wherein the strength of the synapses is enhanced by either change in the number, increase in the efficacy by phosphorylation or change in the type of receptors. Phosphorylation of AMPA receptors changes the localization of the receptors, increases the single channel conductance, and increases the probability of open channel. GluR1 has four phosphorylation sites; serine 818 (S818) is phosphorylated by PKC and is necessary for LTP, serine 831 (S831) is phosphorylated by CaMKII that increases the delivery of receptors to the synapse and also increased their single channel conductance, threonine (T840) is implicated in LTP. Serine 845 (S845) is phosphorylated by PKA which regulates open channel probability. Long term depression is another form of plasticity wherein the number of AMPA receptors is diminished by either phosphorylation of GluR2 at Ser880 or dephosphorylation of GluR1 by protein phosphatase1, protein phosphatase 2A and protein phosphatase 2B (calcineurin).

Literature references

Lee, HK. (2006). Synaptic plasticity and phosphorylation. *Pharmacol Ther, 112*, 810-32. ↗

Kessels, HW., Malinow, R. (2009). Synaptic AMPA receptor plasticity and behavior. *Neuron, 61*, 340-50. ↗

Farrant, M., Cull-Candy, S., Kelly, L. (2006). Regulation of Ca2+-permeable AMPA receptors: synaptic plasticity and beyond. *Curr Opin Neurobiol, 16*, 288-97. ↗

Editions

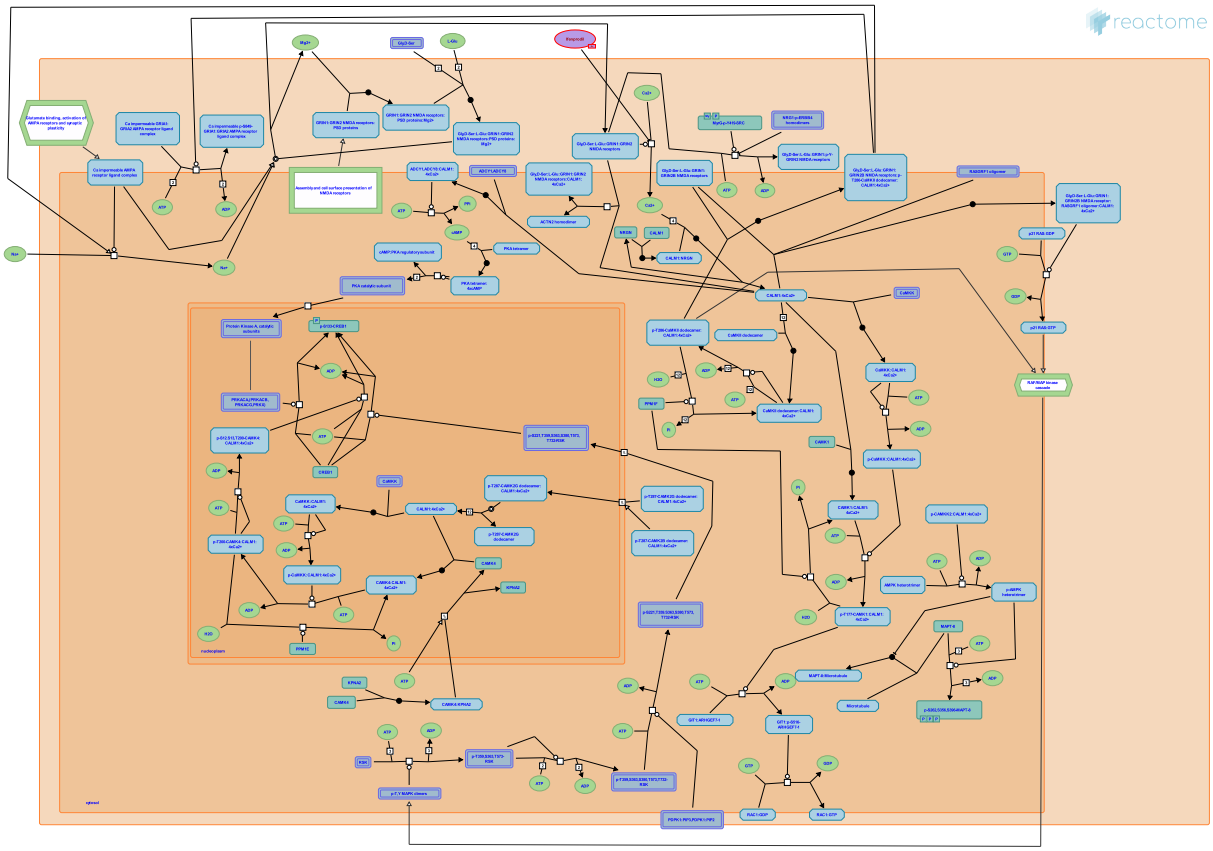
2008-01-14	Authored, Edited	Mahajan, SS.
2009-05-15	Reviewed	Ziff, EB.

Activation of NMDA receptors and postsynaptic events ↗

Location: Neurotransmitter receptors and postsynaptic signal transmission

Stable identifier: R-HSA-442755

Compartments: nucleoplasm, plasma membrane, extracellular region, cytosol



NMDA receptors are a subtype of ionotropic glutamate receptors that are specifically activated by a glutamate agonist N-methyl-D-aspartate (NMDA). Activation of NMDA receptors involves opening of the ion channel that allows the influx of Ca2+. NMDA receptors are central to activity dependent changes in synaptic strength and are predominantly involved in the synaptic plasticity that pertains to learning and memory. A unique feature of NMDA receptors, unlike other glutamate receptors, is the requirement for dual activation, both voltage-dependent and ligand-dependent activation. The ligand-dependent activation of NMDA receptors requires co-activation by two ligands, glutamate and glycine. However, at resting membrane potential, the pore of ligand-bound NMDA receptors is blocked by Mg2+. The voltage dependent Mg2+ block is relieved upon depolarization of the post-synaptic membrane. NMDA receptors are coincidence detectors, and are activated only if there is a simultaneous activation of both pre- and post-synaptic cell. Upon activation, NMDA receptors allow the influx of Ca2+ that initiates various molecular signaling cascades involved in the processes of learning and memory. For review, please refer to Cohen and Greenberg 2008, Hardingham and Bading 2010, Traynelis et al. 2010, and Paoletti et al. 2013.

Literature references

Hardingham, GE., Bading, H. (2010). Synaptic versus extrasynaptic NMDA receptor signalling: implications for neurodegenerative disorders. *Nat. Rev. Neurosci., 11*, 682-96. ↗

Cohen, S., Greenberg, ME. (2008). Communication between the synapse and the nucleus in neuronal development, plasticity, and disease. *Annu Rev Cell Dev Biol, 24*, 183-209. ↗

Myers, SJ., Dingledine, R., Ogden, KK., Wollmuth, LP., Menniti, FS., Hansen, KB. et al. (2010). Glutamate receptor ion channels: structure, regulation, and function. *Pharmacol. Rev., 62*, 405-96. ↗

Zhou, Q., Paoletti, P., Bellone, C. (2013). NMDA receptor subunit diversity: impact on receptor properties, synaptic plasticity and disease. *Nat. Rev. Neurosci., 14*, 383-400. ↗

Editions

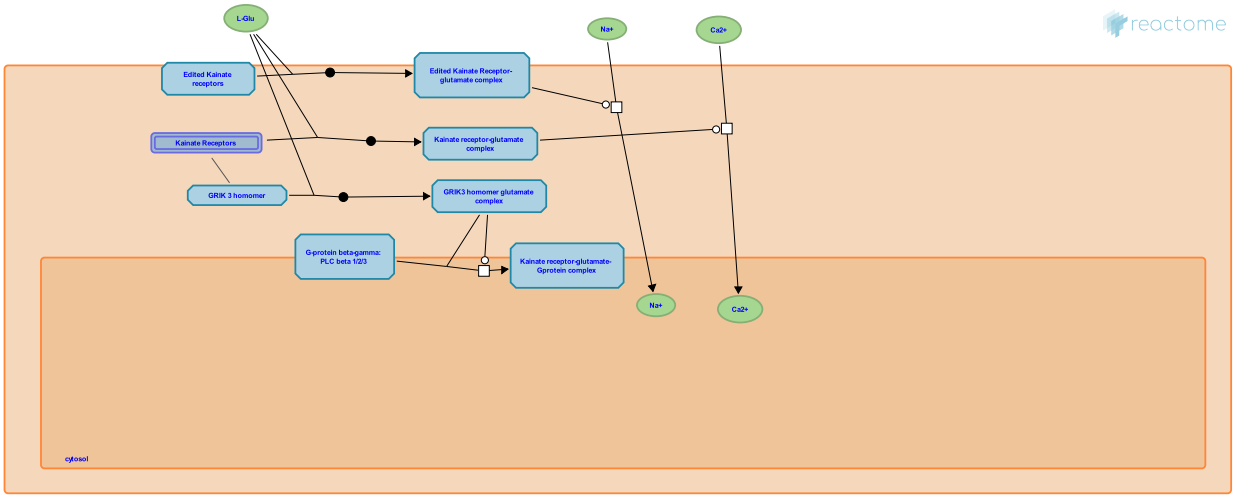
2009-10-29	Authored	Mahajan, SS.
2009-11-18	Reviewed	Tukey, D.
2009-11-19	Edited	Gillespie, ME.
2018-10-10	Authored, Revised	Orlic-Milacic, M.
2018-11-02	Reviewed	Hansen, KB., Yi, F.
2018-11-07	Edited	Orlic-Milacic, M.

Activation of kainate receptors upon glutamate binding ↗

Location: Neurotransmitter receptors and postsynaptic signal transmission

Stable identifier: R-HSA-451326

Compartments: plasma membrane, extracellular region, cytosol



Kainate receptors are found both in the presynaptc terminals and the postsynaptic neurons.
Kainate receptor activation could lead to either ionotropic activity (influx of Ca2+ or Na+ and K+) in the postsynaptic neuron or coupling of the receptor with G proteins in the presynaptic and the postsynaptic neurons.
Kainate receptors are tetramers made from subunits GRIK1-5 or GluR5-7 and KA1-2. Activation of kainate receptors made from GRIK1 or KA2 release Ca2+ from the intracellular stores in a G protein-dependent manner. The G protein involved in this process is sensitive to pertussis toxin.

Literature references

Jane, DE., Lodge, D., Collingridge, GL. (2009). Kainate receptors: pharmacology, function and therapeutic potential. *Neuropharmacology, 56*, 90-113. ↗

Editions

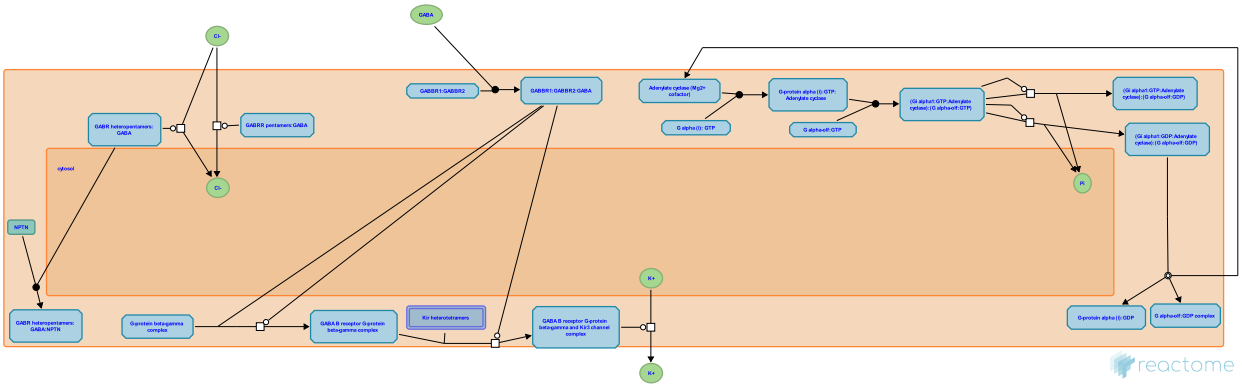
2009-11-18	Reviewed	Tukey, D.
2010-01-15	Authored	Mahajan, SS.
2010-02-06	Edited	Gillespie, ME.

GABA receptor activation ↗

Location: Neurotransmitter receptors and postsynaptic signal transmission

Stable identifier: R-HSA-977443

Compartments: plasma membrane, extracellular region, cytosol



Gamma aminobutyric acid (GABA) receptors are the major inhibitory receptors in human synapses. They are of two types. GABA A receptors are fast-acting ligand gated chloride ion channels that mediate membrane depolarization and thus inhibit neurotransmitter release (G Michels et al Crit Rev Biochem Mol Biol 42, 2007, 3-14). GABA B receptors are slow acting metabotropic Gprotein coupled receptors that act via the inhibitory action of their Galpha/Go subunits on adenylate cyclase to attenuate the actions of PKA. In addition, their Gbeta/gamma subunits interact directly with N and P/Q Ca2+ channels to decrease the release of Ca2+. GABA B receptors also interact with Kir3 K+ channels and increase the influx of K+, leading to cell membrane hyperpolarization and inhibition of channels such as NMDA receptors (A Pinard et al Adv Pharmacol, 58, 2010, 231-55).

Literature references

Slesinger, PA., Padgett, CL. (2010). GABAB receptor coupling to G-proteins and ion channels. *Adv Pharmacol, 58*, 123-47. ↗

Michels, G., Moss, SJ. (2007). GABAA receptors: properties and trafficking. *Crit Rev Biochem Mol Biol, 42*, 3-14. ↗

Bettler, B., Kaupmann, K., Gassmann, M., Mosbacher, J. (2004). Molecular structure and physiological functions of GABA(B) receptors. *Physiol Rev, 84*, 835-67. ↗

Smart, TG., Moss, SJ. (2001). Constructing inhibitory synapses. *Nat Rev Neurosci, 2*, 240-50. ↗

Bettler, B., Pinard, A., Seddik, R. (2010). GABAB receptors: physiological functions and mechanisms of diversity. *Adv Pharmacol, 58*, 231-55. ↗

Editions

2008-11-27	Reviewed	Restituito, S.
2010-11-08	Authored	Mahajan, SS.
2010-11-25	Edited	D'Eustachio, P.

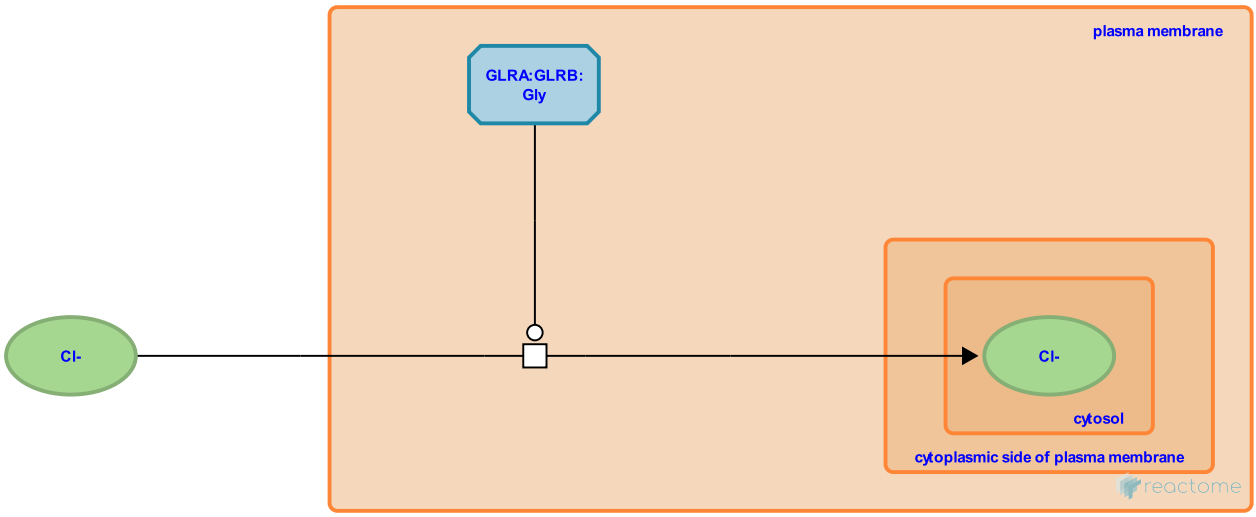
GLRA:GLRB:Gly transports extracellular Cl- to cytosol ↗

Location: Neurotransmitter receptors and postsynaptic signal transmission

Stable identifier: R-HSA-975389

Type: transition

Compartments: plasma membrane



The glycine receptor (GLR) is a ligand-gated ion channel. It is functional as a heteropentamer, consisting of alpha (GLRA) and beta (GLRB) subunits. With no ligand bound, the receptor complex is closed to chloride ions. Binding of the inhibitory neurotransmitter glycine (Gly) to this receptor complex increases chloride conductance into neurons and thus produces hyperpolarization (inhibition of neuronal firing) (Grenningloh et al. 1990, Nikolic et al. 1998, Handford et al. 1996).

Literature references

Becker, CM., Grenningloh, G., Schofield, PR., Betz, H., Siddique, T., Schmieden, V. et al. (1990). Alpha subunit variants of the human glycine receptor: primary structures, functional expression and chromosomal localization of the corresponding genes. *EMBO J, 9*, 771-6. ↗

Becker, CM., Poustka, A., Laube, B., Nikolic, Z., Lichter, P., Mülhardt, C. et al. (1998). The human glycine receptor subunit alpha3. Glra3 gene structure, chromosomal localization, and functional characterization of alternative transcripts. *J Biol Chem, 273*, 19708-14. ↗

Baker, E., Schofield, PR., Sutherland, GR., Handford, CA., Ford, JH., Webb, GC. et al. (1996). The human glycine receptor beta subunit: primary structure, functional characterisation and chromosomal localisation of the human and murine genes. *Brain Res Mol Brain Res, 35*, 211-9. ↗

Editions

2010-09-24	Authored, Edited	Jassal, B.
2010-11-15	Reviewed	He, L.

NBEA binds GLRB ↗

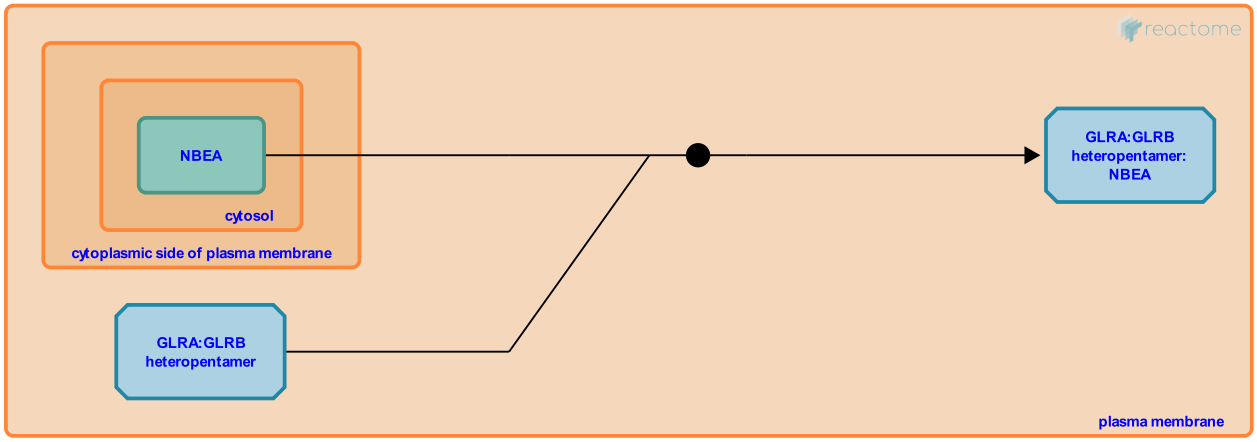
Location: Neurotransmitter receptors and postsynaptic signal transmission

Stable identifier: R-HSA-9673173

Type: binding

Compartments: plasma membrane

Inferred from: Nbea binds Glrb (Rattus norvegicus)



Binding of NBEA to GLRB (glycine receptor beta subunit) was demonstrated by co-immunoprecipitation of recombinant rat Glrb with endogenous Nbea from rat brain, as well as co-immunoprecipitation of recombinant rat Glrb with recombinant mouse Nbea. It was also shown, by immunocytochemistry, that NBEA and glycine receptor co-localize at postsynaptic densities of inhibitory synapses (del Pino et al. 2011). NBEA may be involved in trafficking of glycine receptors to the plasma membrane. As glycine receptors are pre-assembled at the endoplasmic reticulum (Griffon et al. 1999), the reaction diagram depicts binding of NBEA to this pre-assembled receptor complex, consisting of glycine receptor alpha and beta subunits.

Editions

2020-01-07	Authored	Orlic-Milacic, M.
2020-02-10	Reviewed	Martin, EA., Miller, AC.
2020-02-20	Edited	Orlic-Milacic, M.

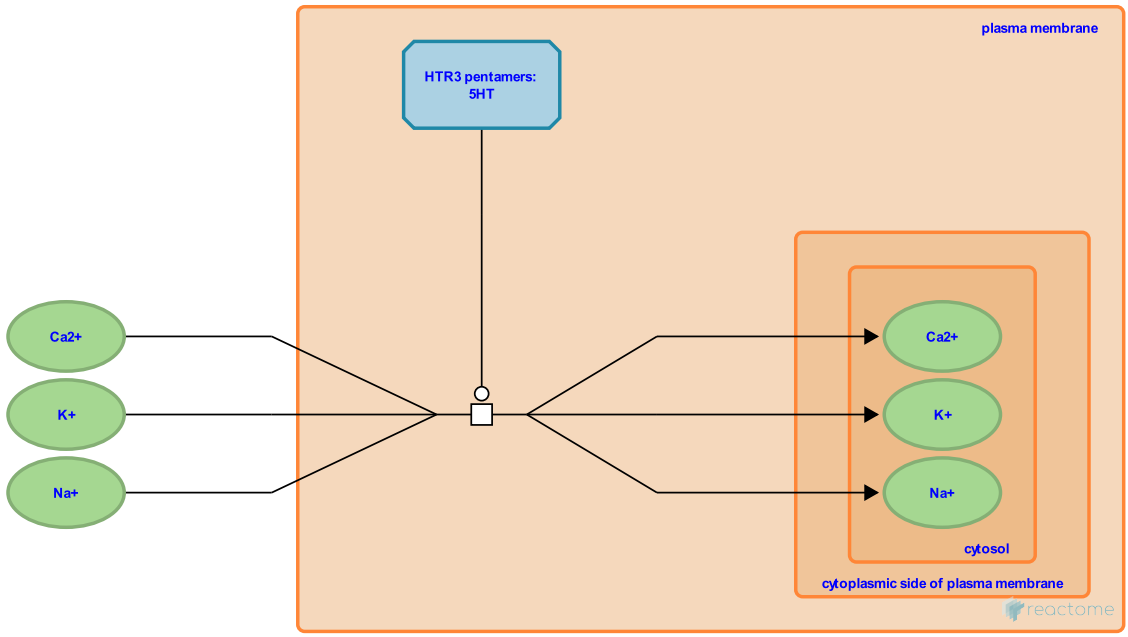
HTR3 pentamers:5HT transport Na+,K+,Ca2+ ↗

Location: Neurotransmitter receptors and postsynaptic signal transmission

Stable identifier: R-HSA-975311

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



The 5-hydroxytryptamine receptor (HTR3) family are members of the superfamily of ligand-gated ion channels (LGICs). Five receptors (HTR3A-E) can form a homopentamer (HTR3A) or heteropentamers (HTR3A with B, C, D or E) (Barrera et al. 2005, Niesler et al. 2007; reviews - Barnes et al. 2009, Wu et al. 2015) Although heterpentamer composition can vary between the two receptors binding, the example 2xHTR3A:3xHTR3(B-E) is shown here. Binding of the neurotransmitter 5-hydroxytryptamine (5HT, serotonin) to the HTR3 complex opens the channel, which in turn, leads to an excitatory response in neurons and is permeable to sodium, potassium, and calcium ions (Miyake et al. 1995, Davies et al. 1999).

Literature references

Kirkness, EF., Peters, JA., Davies, PA., Pistis, M., Hales, TG., Lambert, JJ. et al. (1999). The 5-HT3B subunit is a major determinant of serotonin-receptor function. *Nature, 397*, 359-63. ↗

Jiang, Y., Cheng, H., Wu, ZS., Melcher, K., Xu, HE. (2015). Ion channels gated by acetylcholine and serotonin: structures, biology, and drug discovery. *Acta Pharmacol. Sin., 36*, 895-907. ↗

Moller, D., Walstab, J., Rietdorf, J., Kapeller, J., Niesler, B., Combrink, S. et al. (2007). Characterization of the novel human serotonin receptor subunits 5-HT3C,5-HT3D, and 5-HT3E. *Mol Pharmacol, 72*, 8-17. ↗

Peters, JA., Barnes, NM., Lummis, SC., Hales, TG. (2009). The 5-HT3 receptor--the relationship between structure and function. *Neuropharmacology, 56*, 273-84. ↗

Henderson, RM., Herbert, P., Martin, IL., Edwardson, JM., Barrera, NP. (2005). Atomic force microscopy reveals the stoichiometry and subunit arrangement of 5-HT3 receptors. *Proc. Natl. Acad. Sci. U.S.A., 102*, 12595-600. ↗

Editions

2010-09-23	Authored, Edited	Jassal, B.
2010-11-15	Reviewed	He, L.

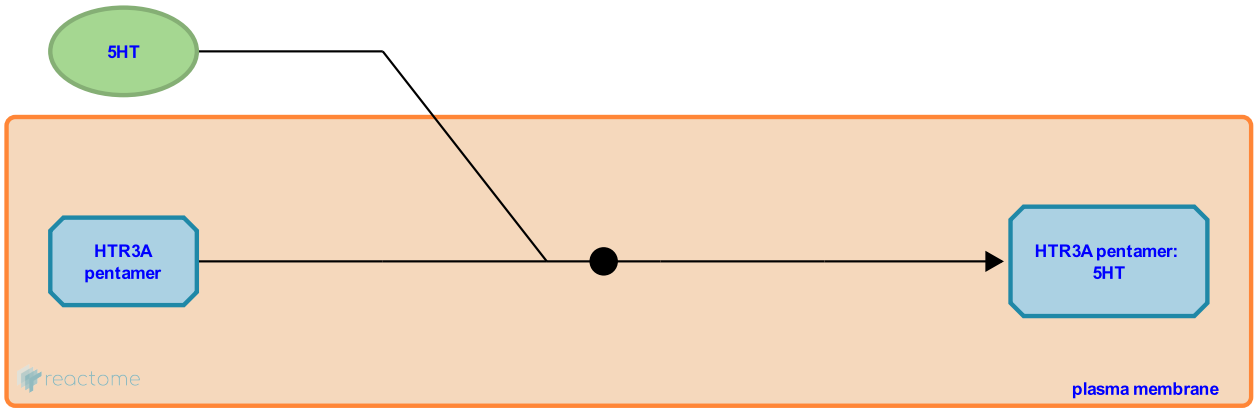
HTR3A pentamer binds 5HT ↗

Location: Neurotransmitter receptors and postsynaptic signal transmission

Stable identifier: R-HSA-9649108

Type: binding

Compartments: plasma membrane, extracellular region



The 5-hydroxytryptamine receptor (HTR3) family are members of the superfamily of ligand-gated ion channels (LGICs). Five receptors (HTR3A-E) can form a homopentamer (HTR3A) or heteropentamers (HTR3A with B, C, D or E) (Barrera et al. 2005, Niesler et al. 2007; reviews - Barnes et al. 2009, Wu et al. 2015). Binding of the neurotransmitter 5-hydroxytryptamine (5HT, serotonin) to the HTR3 pentamer opens the channel making it permeable to sodium, potassium, and calcium ions, which in turn leads to an excitatory response in neurons (Miyake et al. 1995, Davies et al. 1999).

Literature references

Kirkness, EF., Peters, JA., Davies, PA., Pistis, M., Hales, TG., Lambert, JJ. et al. (1999). The 5-HT3B subunit is a major determinant of serotonin-receptor function. *Nature, 397*, 359-63. ↗

Jiang, Y., Cheng, H., Wu, ZS., Melcher, K., Xu, HE. (2015). Ion channels gated by acetylcholine and serotonin: structures, biology, and drug discovery. *Acta Pharmacol. Sin., 36*, 895-907. ↗

Moller, D., Walstab, J., Rietdorf, J., Kapeller, J., Niesler, B., Combrink, S. et al. (2007). Characterization of the novel human serotonin receptor subunits 5-HT3C,5-HT3D, and 5-HT3E. *Mol Pharmacol, 72*, 8-17. ↗

Peters, JA., Barnes, NM., Lummis, SC., Hales, TG. (2009). The 5-HT3 receptor--the relationship between structure and function. *Neuropharmacology, 56*, 273-84. ↗

Henderson, RM., Herbert, P., Martin, IL., Edwardson, JM., Barrera, NP. (2005). Atomic force microscopy reveals the stoichiometry and subunit arrangement of 5-HT3 receptors. *Proc. Natl. Acad. Sci. U.S.A., 102*, 12595-600. ↗

Editions

2010-09-23	Authored, Edited	Jassal, B.
2010-11-15	Reviewed	He, L.

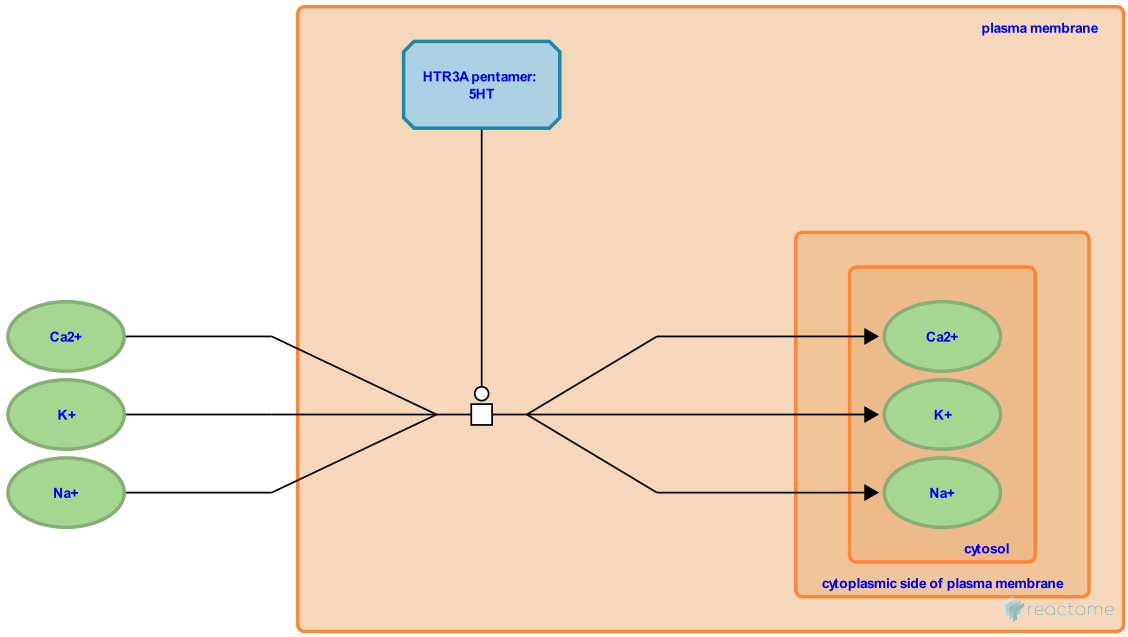
HTR3A pentamer:5HT transports Na+,K+,Ca2+ ↗

Location: Neurotransmitter receptors and postsynaptic signal transmission

Stable identifier: R-HSA-9648983

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



The 5-hydroxytryptamine receptor (HTR3) family are members of the superfamily of ligand-gated ion channels (LGICs). Five receptors (HTR3A-E) can form a homopentamer (HTR3A) or heteropentamers (HTR3A with B, C, D or E) (Barrera et al. 2005, Niesler et al. 2007; reviews - Barnes et al. 2009, Wu et al. 2015). Binding of the neurotransmitter 5-hydroxytryptamine (5HT, serotonin) to the HTR3 pentamer opens the channel making it permeable to sodium, potassium, and calcium ions, which in turn leads to an excitatory response in neurons (Miyake et al. 1995, Davies et al. 1999).

Literature references

Kirkness, EF., Peters, JA., Davies, PA., Pistis, M., Hales, TG., Lambert, JJ. et al. (1999). The 5-HT3B subunit is a major determinant of serotonin-receptor function. *Nature, 397*, 359-63. ↗

Jiang, Y., Cheng, H., Wu, ZS., Melcher, K., Xu, HE. (2015). Ion channels gated by acetylcholine and serotonin: structures, biology, and drug discovery. *Acta Pharmacol. Sin., 36*, 895-907. ↗

Moller, D., Walstab, J., Rietdorf, J., Kapeller, J., Niesler, B., Combrink, S. et al. (2007). Characterization of the novel human serotonin receptor subunits 5-HT3C,5-HT3D, and 5-HT3E. *Mol Pharmacol, 72*, 8-17. ↗

Peters, JA., Barnes, NM., Lummis, SC., Hales, TG. (2009). The 5-HT3 receptor--the relationship between structure and function. *Neuropharmacology, 56*, 273-84. ↗

Henderson, RM., Herbert, P., Martin, IL., Edwardson, JM., Barrera, NP. (2005). Atomic force microscopy reveals the stoichiometry and subunit arrangement of 5-HT3 receptors. *Proc. Natl. Acad. Sci. U.S.A., 102*, 12595-600. ↗

Editions

2010-09-23	Authored, Edited	Jassal, B.
2010-11-15	Reviewed	He, L.

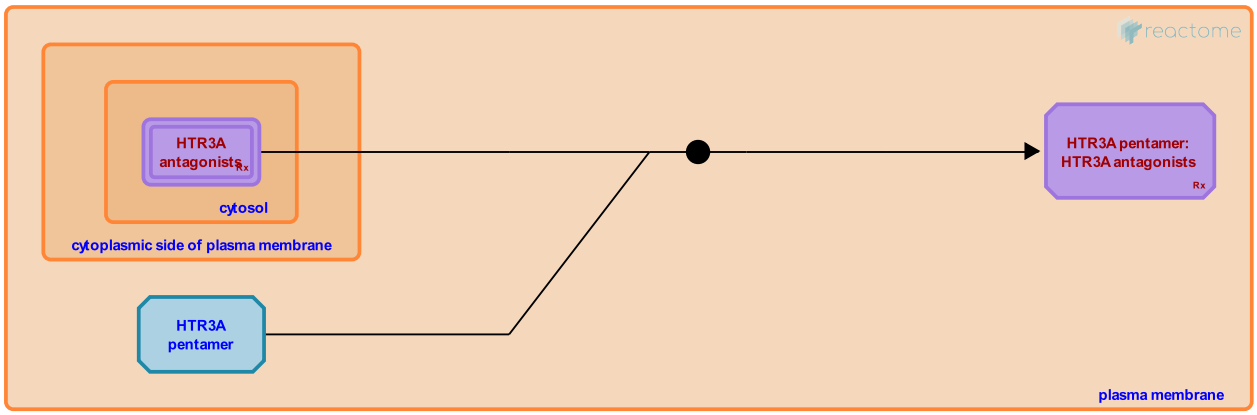
HTR3A antagonists bind HTR3A pentamer ↗

Location: Neurotransmitter receptors and postsynaptic signal transmission

Stable identifier: R-HSA-9648949

Type: binding

Compartments: plasma membrane, extracellular region



5-hydroxytryptamine receptors 3A (HTR3As, 5-HT3) are present in several critical sites in the CNS involved in emesis and are involved in the integration of the vomiting reflex, pain processing, anxiety control and the reward system. Serotonin (5HT) is released by enterochromaffin cells of the small intestine in response to chemotherapeutic agents which may stimulate vagal afferents (via HTR3A receptors) to initiate the vomiting reflex. 5-HT3 antagonist drugs suppress vomiting and nausea by inhibiting serotonin binding to HTR3A receptors (Tyers & Freeman 1992). 5-HT3 antagonists are widely used for relieving chemotherapy-induced vomiting (Gilmore et al. 2018) as well as radiotherapy-induced and post-operative nausea and vomiting.

5-HT3 antagonists are informally known as "setrons" and are a class of drugs that act as receptor antagonists at the HTR3A receptor. With the exceptions of alosetron and cilansetron, which are used in the treatment of irritable bowel syndrome, all 5-HT3 antagonists are antiemetics, used in the prevention and treatment of nausea and vomiting. 5-HT3 antagonists, although sharing the same mechanism of action, have different chemical structures which lends itself to different affinities for the receptor, dose response, duration of action and different metabolic routes via the cytochrome P450 system. Due to these differences, patients resistant to one antagonist may respond well to another (Gan 2005).

Ondansetron (brand name Zofran) was the first 5-HT3 antagonist, developed by Glaxo in 1984 and approved by the U.S. FDA in 1991 (Griddine & Bush 2019). It is also available in several other countries, including the UK, Ireland, Australia, Canada, France and Brazil. Ondansetron is used to prevent nausea and vomiting caused by cancer chemotherapy, radiation therapy, or surgery (Markham & Sorkin 1993) and is also useful in gastroenteritis therapy (Schnadower et al. 2015). Granisetron (trade name Kytril) is a serotonin 5-HT3 receptor antagonist used as an antiemetic to treat nausea and vomiting following chemotherapy and radiotherapy. The drug was approved in the United Kingdom in 1991 and in the United States in 1994. Granisetron is metabolized slowly by the liver, giving it a longer than average half-life (Hsu 2010).

Approved in 2003 by the FDA, palonosetron (trade name Aloxi) is a second generation 5-HT3 receptor antagonist. Unlike the first generation 5-HT3 receptor antagonists, palonosetron demonstrates efficacy in preventing both acute and delayed emesis (Navari 2014). Tropisetron (trade name Navoban) is a serotonin 5-HT3 receptor antagonist used mainly as an antiemetic to treat nausea and vomiting following chemotherapy (Lee et al. 1993). It was approved for medical use in 1992 in Europe, Australia, New Zealand, Japan, South Korea and the Philippines but is not available in the U.S.

Ramosetron is a serotonin 5-HT3 receptor antagonist for the treatment of nausea and vomiting (Rabasseda 2002) and for a treatment of diarrhea-predominant irritable bowel syndrome (Hirata et al. 2007, Min & Rhee 2015). It is only licensed for use in Japan and selected Southeast Asian countries and in India. Alosetron (brand name Lotronex) has an antagonist action on the 5-HT3 receptors of the enteric nervous system of the GI tract. It is not classified or approved as an antiemetic, instead, it is used for the management of severe diarrhea-predominant irritable bowel syndrome (IBS) in women only (Lacy et al. 2018). It was withdrawn from the market in 2000 due to serious life-threatening gastrointestinal adverse effects (Camilleri et al. 2001), but was reintroduced in 2002 with restricted availability and use (Lucak 2010).

Cilansetron is the first 5-HT3 antagonist specifically designed for IBS that is effective in men as well as women (Olden & Crowell 2005, Zheng et al. 2017). The drug is not available in the U.S. but the manufacturer, Solvay, is in discussion with the MHRA (UK) and EU regulators. Azasetron is an antiemetic which acts as a 5-HT3 receptor antagonist used in the management of nausea and vomiting induced by cancer chemotherapy (Endo et al. 2012). It is approved for marketing in Japan under the trade name Serotone.

Literature references

Sorkin, EM., Markham, A. (1993). Ondansetron. An update of its therapeutic use in chemotherapy-induced and post-operative nausea and vomiting. *Drugs, 45*, 931-952. ↗

Tyers, MB., Freeman, AJ. (1992). Mechanism of the anti-emetic activity of 5-HT3 receptor antagonists. *Oncology, 49*, 263-8. ↗

Chuang, E., Nicandro, JP., Earnest, DL., Lacy, BE. (2018). Alosetron use in clinical practice: significant improvement in irritable bowel syndrome symptoms evaluated using the US Food and Drug Administration composite end-point. *Therap Adv Gastroenterol, 11*, 1756284818771674. ↗

Lucak, SL. (2010). Optimizing outcomes with alosetron hydrochloride in severe diarrhea-predominant irritable bowel syndrome. *Therap Adv Gastroenterol, 3*, 165-72. ↗

Keto, Y., Hirata, T., Sasamata, M., Akuzawa, S., Funatsu, T. (2007). Evaluation of the pharmacological profile of ramosetron, a novel therapeutic agent for irritable bowel syndrome. *J. Pharmacol. Sci., 104*, 263-73. ↗

Editions

2019-06-10	Authored, Edited	Jassal, B.
2022-03-01	Reviewed	Huddart, R.
2022-05-10	Edited	Matthews, L.

Table of Contents