



Pathway Analysis Report

This report contains the pathway analysis results for the submitted sample ". Analysis was performed against Reactome version 78 on 30/11/2021. The web link to these results is:

<https://reactome.org/PathwayBrowser/#/ANALYSIS=MjAyMTEzMzAxMzUxMTVfNjAwNg%3D%3D>

Please keep in mind that analysis results are temporarily stored on our server. The storage period depends on usage of the service but is at least 7 days. As a result, please note that this URL is only valid for a limited time period and it might have expired.

Table of Contents

1. Introduction
2. Properties
3. Genome-wide overview
4. Most significant pathways
5. Pathways details
6. Identifiers found
7. Identifiers not found

1. Introduction

Reactome is a curated database of pathways and reactions in human biology. Reactions can be considered as pathway 'steps'. Reactome defines a 'reaction' as any event in biology that changes the state of a biological molecule. Binding, activation, translocation, degradation and classical biochemical events involving a catalyst are all reactions. Information in the database is authored by expert biologists, entered and maintained by Reactome's team of curators and editorial staff. Reactome content frequently cross-references other resources e.g. NCBI, Ensembl, UniProt, KEGG (Gene and Compound), ChEBI, PubMed and GO. Orthologous reactions inferred from annotation for *Homo sapiens* are available for 17 non-human species including mouse, rat, chicken, puffer fish, worm, fly, yeast, rice, and *Arabidopsis*. Pathways are represented by simple diagrams following an SBGN-like format.

Reactome's annotated data describe reactions possible if all annotated proteins and small molecules were present and active simultaneously in a cell. By overlaying an experimental dataset on these annotations, a user can perform a pathway over-representation analysis. By overlaying quantitative expression data or time series, a user can visualize the extent of change in affected pathways and its progression. A binomial test is used to calculate the probability shown for each result, and the p-values are corrected for the multiple testing (Benjamini–Hochberg procedure) that arises from evaluating the submitted list of identifiers against every pathway.

To learn more about our Pathway Analysis, please have a look at our relevant publications:

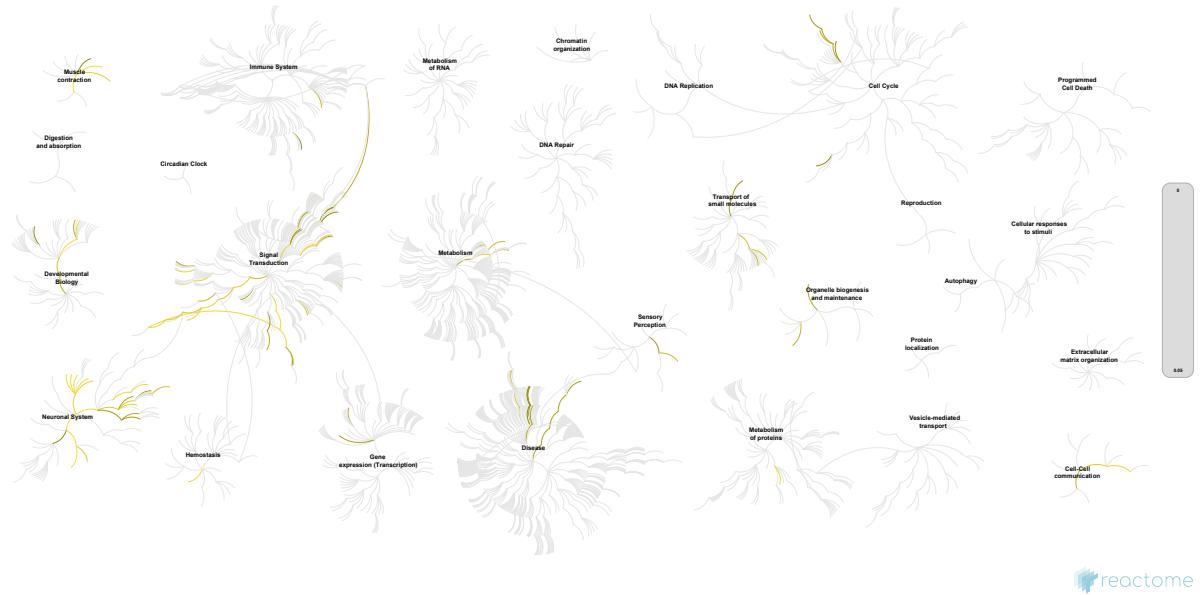
Fabregat A, Sidiropoulos K, Garapati P, Gillespie M, Hausmann K, Haw R, ... D'Eustachio P (2016). The reactome pathway knowledgebase. *Nucleic Acids Research*, 44(D1), D481–D487. <https://doi.org/10.1093/nar/gkv1351>.

Fabregat A, Sidiropoulos K, Viteri G, Forner O, Marin-Garcia P, Arnau V, ... Hermjakob H (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC Bioinformatics*, 18.

2. Properties

- This is an **overrepresentation** analysis: A statistical (hypergeometric distribution) test that determines whether certain Reactome pathways are over-represented (enriched) in the submitted data. It answers the question 'Does my list contain more proteins for pathway X than would be expected by chance?' This test produces a probability score, which is corrected for false discovery rate using the Benjamani-Hochberg method. ↗
- 381 out of 514 identifiers in the sample were found in Reactome, where 1318 pathways were hit by at least one of them.
- All non-human identifiers have been converted to their human equivalent. ↗
- This report is filtered to show only results for species 'Homo sapiens' and resource 'all resources'.
- The unique ID for this analysis (token) is MjAyMTExMzAxMzUxMTVfNjAwNg%3D%3D. This ID is valid for at least 7 days in Reactome's server. Use it to access Reactome services with your data.

3. Genome-wide overview



This figure shows a genome-wide overview of the results of your pathway analysis. Reactome pathways are arranged in a hierarchy. The center of each of the circular "bursts" is the root of one top-level pathway, for example "DNA Repair". Each step away from the center represents the next level lower in the pathway hierarchy. The color code denotes over-representation of that pathway in your input dataset. Light grey signifies pathways which are not significantly over-represented.

4. Most significant pathways

The following table shows the 25 most relevant pathways sorted by p-value.

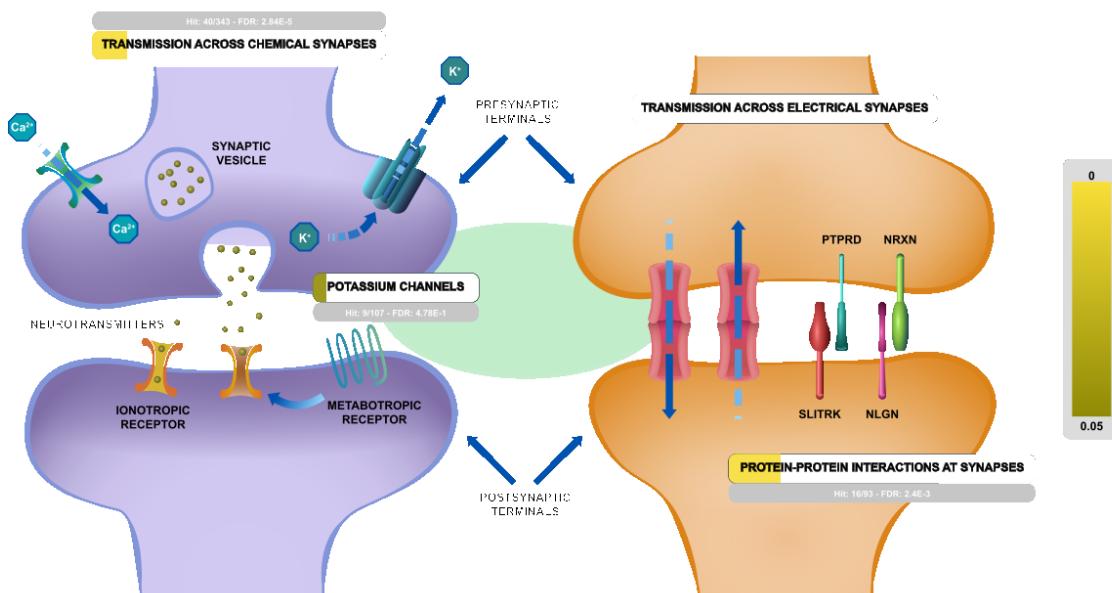
Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
Neuronal System	57 / 489	0.034	4.53e-11	6.62e-08	135 / 216	0.016
Transmission across Chemical Synapses	40 / 343	0.024	3.88e-08	2.84e-05	107 / 163	0.012
Protein-protein interactions at synapses	16 / 93	0.007	5.37e-06	0.002	24 / 33	0.002
Neurotransmitter receptors and postsynaptic signal transmission	27 / 232	0.016	6.58e-06	0.002	84 / 109	0.008
Dopamine Neurotransmitter Release Cycle	7 / 28	0.002	2.77e-04	0.081	3 / 5	3.68e-04
Neurexins and neuroligins	10 / 60	0.004	3.87e-04	0.094	15 / 19	0.001
Cardiac conduction	16 / 138	0.01	5.01e-04	0.098	14 / 27	0.002
Serotonin Neurotransmitter Release Cycle	6 / 23	0.002	6.02e-04	0.098	2 / 4	2.95e-04
Glutamate Neurotransmitter Release Cycle	7 / 32	0.002	6.07e-04	0.098	4 / 8	5.89e-04
L1CAM interactions	15 / 130	0.009	7.76e-04	0.103	13 / 54	0.004
Neuropophilin interactions with VEGF and VEGFR	3 / 4	2.80e-04	7.79e-04	0.103	2 / 2	1.47e-04
Phase 0 - rapid depolarisation	7 / 34	0.002	8.62e-04	0.104	2 / 2	1.47e-04
Adenosine P1 receptors	3 / 5	3.50e-04	0.001	0.165	2 / 2	1.47e-04
Norepinephrine Neurotransmitter Release Cycle	6 / 30	0.002	0.002	0.211	3 / 6	4.42e-04
Insulin processing	6 / 30	0.002	0.002	0.211	3 / 16	0.001
Dopamine receptors	3 / 6	4.20e-04	0.002	0.211	3 / 3	2.21e-04
DAG and IP3 signaling	8 / 53	0.004	0.003	0.211	22 / 28	0.002
Activation of Ca-permeable Kainate Receptor	4 / 13	9.11e-04	0.003	0.211	2 / 2	1.47e-04
CaM pathway	7 / 43	0.003	0.003	0.211	20 / 24	0.002
Calmodulin induced events	7 / 43	0.003	0.003	0.211	19 / 23	0.002
Ionotropic activity of kainate receptors	4 / 14	9.81e-04	0.004	0.215	2 / 4	2.95e-04
Dissolution of Fibrin Clot	4 / 14	9.81e-04	0.004	0.215	8 / 19	0.001
NrCAM interactions	3 / 7	4.91e-04	0.004	0.22	4 / 4	2.95e-04
Signaling by FGFR2 IIIa TM	5 / 24	0.002	0.004	0.242	2 / 2	1.47e-04
Opioid Signalling	12 / 113	0.008	0.005	0.242	39 / 59	0.004

* False Discovery Rate

5. Pathways details

For every pathway of the most significant pathways, we present its diagram, as well as a short summary, its bibliography and the list of inputs found in it.

1. Neuronal System (R-HSA-112316)



The human brain contains at least 100 billion neurons, each with the ability to influence many other cells. Clearly, highly sophisticated and efficient mechanisms are needed to enable communication among this astronomical number of elements. This communication occurs across synapses, the functional connection between neurons. Synapses can be divided into two general classes: electrical synapses and chemical synapses. Electrical synapses permit direct, passive flow of electrical current from one neuron to another. The current flows through gap junctions, specialized membrane channels that connect the two cells. Chemical synapses enable cell-to-cell communication using neurotransmitter release. Neurotransmitters are chemical agents released by presynaptic neurons that trigger a secondary current flow in postsynaptic neurons by activating specific receptor molecules. Neurotransmitter secretion is triggered by the influx of Ca^{2+} through voltage-gated channels, which gives rise to a transient increase in Ca^{2+} concentration within the presynaptic terminal. The rise in Ca^{2+} concentration causes synaptic vesicles (the presynaptic organelles that store neurotransmitters) to fuse with the presynaptic plasma membrane and release their contents into the space between the pre- and postsynaptic cells.

References

Fitzpatrick D, Augustine DJ, Katz LC, Williams JM, Purves D, McNamara JO & LaMantia AS (2001). *Neuroscience 2nd Edition*.

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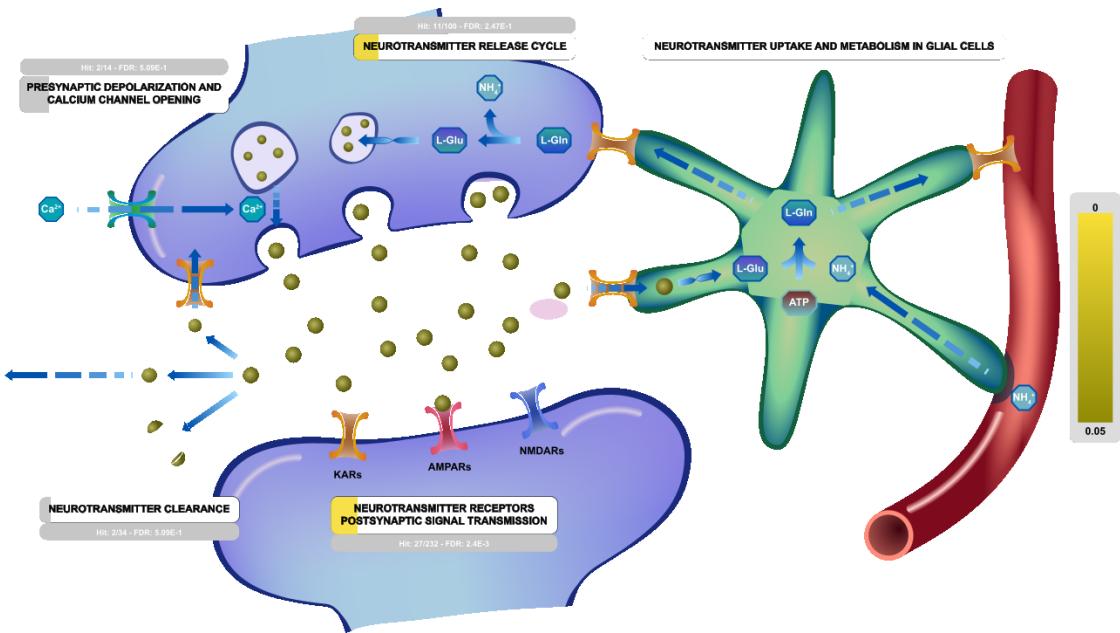
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2004-04-22	Created	Joshi-Tope G
2005-11-10	Edited	Gillespie ME

Date	Action	Author
2005-11-10	Authored	Gillespie ME
2021-09-10	Modified	Weiser JD

58 submitted entities found in this pathway, mapping to 59 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
1007	Q9P2U7	10089	Q9Y2U2	111	O95622
11141	Q9NZN1	1142	Q05901	170572	Q8WXA8
1739	Q12959	18	P80404	2258	P0DP23
2259	P0DP23	22829	Q8NFZ3	2557	P48169
26122	O43307	26280	Q9NP60	27328	Q15825
2739	Q14957	2742	P23416, Q13255	2899	Q13003
2900	Q16099	2915	P41594	321	Q99767
3359	P46098	3746	P48547	3751	Q9NZV8
3752	Q9UK17	3772	Q99712	3778	Q12791
3949	P63027	4128	P21397	4137	P10636-8
438	P78508	476	Q07001	4916	Q16288
553	Q9NZV8	5575	P31321	5578	P17252
5595	P27361	563	P56696	57497	Q9ULH4
58512	O95886	6196	Q15349	6197	P51812
64130	Q9HAP6	6505	P43005	6532	P31645
6616	P60880	6804	Q16623	6854	Q92777
7102	P41732	774	Q00975	782	Q02641
814	Q16566	815	Q9UQM7	8500	Q13136
9228	Q9P1A6	9256	O95153	9456	Q86YM7
9568	O75899				

2. Transmission across Chemical Synapses (R-HSA-112315)



Chemical synapses are specialized junctions that are used for communication between neurons, neurons and muscle or gland cells. The synapse involves a presynaptic neuron and a postsynaptic neuron, muscle cell or glad cell. The pre and the postsynaptic cell are separated by a gap (space) of 20 to 40 nm called the synaptic cleft. The signals pass in a single direction from the presynaptic to postsynaptic neuron (cell). The presynaptic neuron communicates via the release of neurotransmitter which bind the receptors on the postsynaptic cell. The process is initiated when an action potential invades the terminal membrane of the presynaptic neuron.

Action potentials occur in electrically excitable cells such as neurons and muscles and endocrine cells. They are initiated by the transient opening of voltage dependent sodium channels, causing a rapid, large depolarization of membrane potentials that spread along the axon membrane.

When action potentials arrive at the synaptic terminals, depolarization in membrane potential leads to the opening of voltage gated calcium channels located on the presynaptic membrane. The external Ca²⁺ concentration is approximately 10-3 M while the internal Ca²⁺ concentration is approximately 10-7 M. Opening of calcium channels causes a rapid influx of Ca²⁺ into the presynaptic terminal. The elevated presynaptic Ca²⁺ concentration allows synaptic vesicles to fuse with the plasma membrane of the presynaptic neuron and release their contents, neurotransmitters, into the synaptic cleft. These diffuse across the synaptic cleft and bind to specific receptors on the membrane of the postsynaptic cells. Activation of postsynaptic receptors upon neurotransmitter binding can lead to a multitude of effects in the postsynaptic cell, such as changing the membrane potential and excitability, and triggering intracellular signaling cascades.

References

Fitzpatrick D, Augustine DJ, Katz LC, Williams JM, Purves D, McNamara JO & LaMantia AS (2001). *Neuroscience 2nd Edition*.

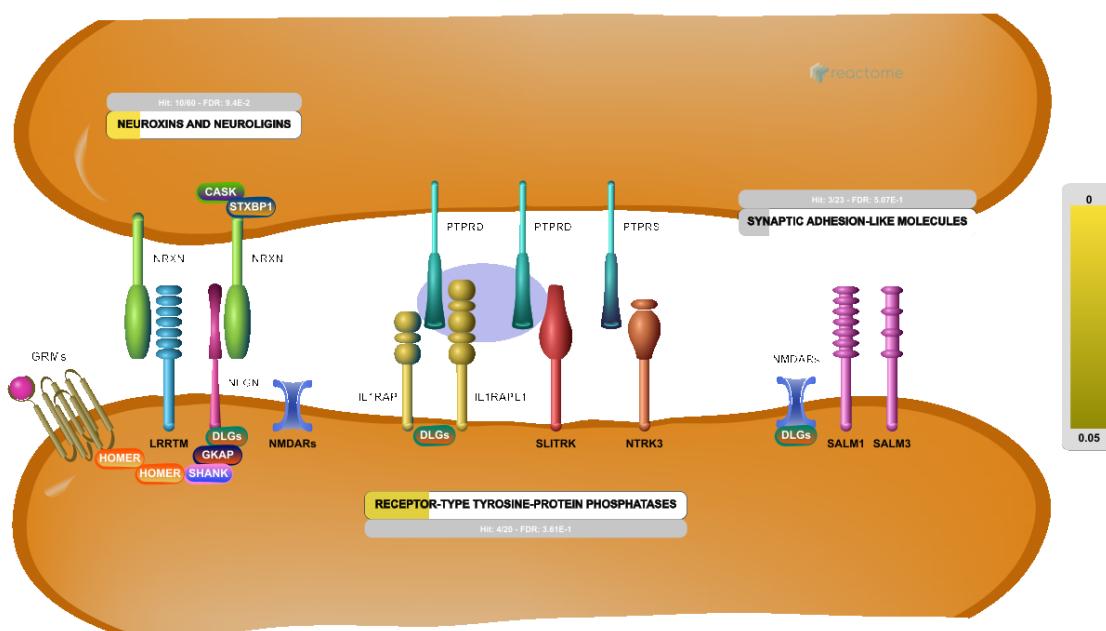
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Date	Action	Author
2004-04-22	Created	Joshi-Tope G
2008-01-14	Edited	Mahajan SS
2008-01-14	Authored	Mahajan SS
2008-12-02	Reviewed	Restituito S, Kavalali E
2020-01-24	Reviewed	Wen H
2021-09-10	Modified	Weiser JD

41 submitted entities found in this pathway, mapping to 41 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
1007	Q9P2U7	111	O95622	1142	Q05901
170572	Q8WXA8	1739	Q12959	18	P80404
2258	P0DP23	2259	P0DP23	2557	P48169
26122	O43307	27328	Q15825	2739	Q14957
2742	P23416	2899	Q13003	2900	Q16099
3359	P46098	3772	Q99712	3949	P63027
4128	P21397	4137	P10636-8	438	P78508
476	Q07001	5575	P31321	5578	P17252
5595	P27361	6196	Q15349	6197	P51812
64130	Q9HAP6	6505	P43005	6532	P31645
6616	P60880	6804	Q16623	6854	Q92777
7102	P41732	774	Q00975	782	Q02641
814	Q16566	815	Q9UQM7	8500	Q13136
9256	O95153	9568	O75899		

3. Protein-protein interactions at synapses (R-HSA-6794362)



Cellular compartments: plasma membrane, cytosol.

Synapses constitute highly specialized sites of asymmetric cell-cell adhesion and intercellular communication. Its formation involves the recruitment of presynaptic and postsynaptic molecules at newly formed contacts. Synapse assembly and maintenance invokes heterophilic presynaptic and postsynaptic transmembrane proteins that bind each other in the extracellular space and recruit additional proteins via their intracellular domains. Members of the cadherin and immunoglobulin (Ig) superfamilies are thought to mediate this function. Several molecules, including synaptic cell-adhesion molecule (SynCAM), N-cadherin, neural cell-adhesion molecule (NCAM), Eph receptor tyrosine kinases, and neuroligins and neurexins, have been implicated in synapse formation and maintenance (Dean & Dresbach 2006, Craig et al. 2006, Craig & Kang 2007, Sudhof 2008).

References

- McClelland AC, Dalva MB & Kayser MS (2007). Cell adhesion molecules: signalling functions at the synapse. *Nat. Rev. Neurosci.*, 8, 206-20. [🔗](#)
- Dresbach T & Dean C (2006). Neuroligins and neurexins: linking cell adhesion, synapse formation and cognitive function. *Trends Neurosci.*, 29, 21-9. [🔗](#)
- Südhof TC (2008). Neuroligins and neurexins link synaptic function to cognitive disease. *Nature*, 455, 903-11. [🔗](#)

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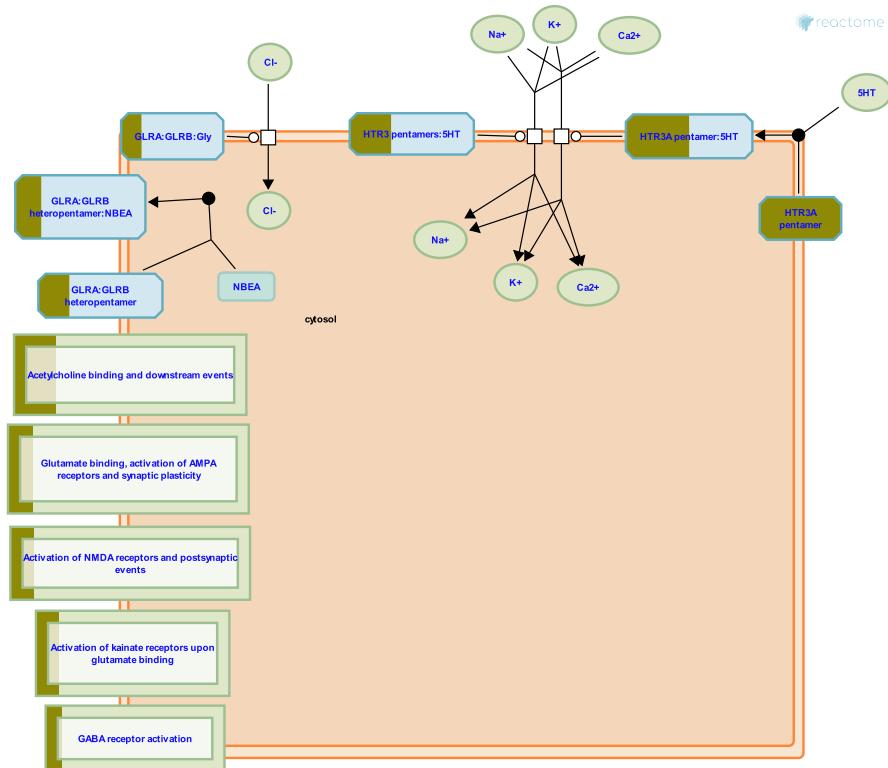
Date	Action	Author
2015-09-04	Edited	Garapati P V
2015-09-04	Authored	Garapati P V
2015-09-04	Created	Garapati P V
2015-11-09	Reviewed	Washbourne P

Date	Action	Author
2021-09-10	Modified	Weiser JD

16 submitted entities found in this pathway, mapping to 16 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
11141	Q9NZN1	1739	Q12959	22829	Q8NFZ3
26280	Q9NP60	2739	Q14957	2742	Q13255
2915	P41594	321	Q99767	4916	Q16288
57497	Q9ULH4	58512	O95886	64130	Q9HAP6
6804	Q16623	8500	Q13136	9228	Q9P1A6
9456	Q86YM7				

4. Neurotransmitter receptors and postsynaptic signal transmission (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.

References

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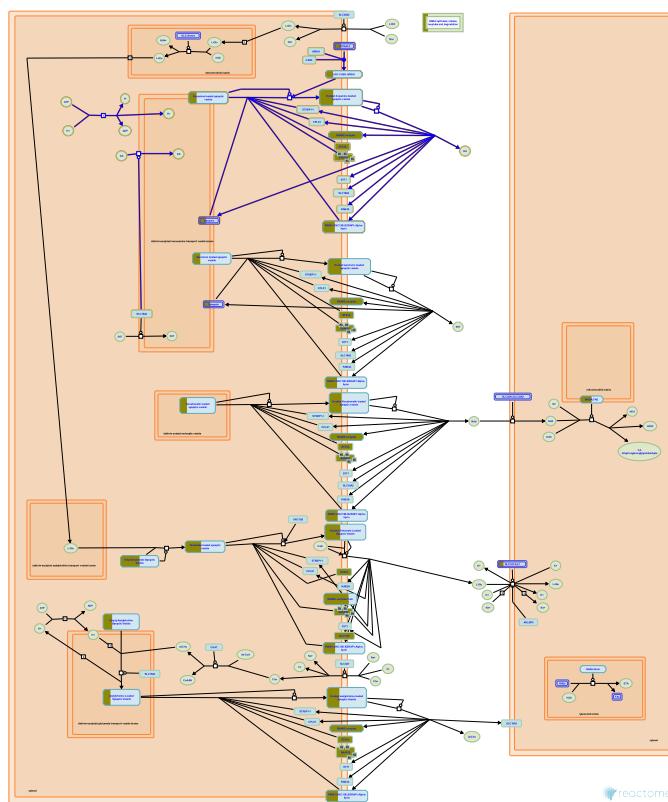
Date	Action	Author
2004-04-22	Created	Joshi-Tope G
2008-01-14	Authored	Mahajan SS
2008-12-02	Reviewed	Restituito S, Kavalali E
2021-09-10	Modified	Weiser JD

28 submitted entities found in this pathway, mapping to 28 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
111	O95622	1142	Q05901	170572	Q8WXAA
1739	Q12959	2258	P0DP23	2259	P0DP23
2557	P48169	26122	O43307	27328	Q15825
2739	Q14957	2742	P23416	2899	Q13003
2900	Q16099	3359	P46098	3772	Q99712
4137	P10636-8	438	P78508	476	Q07001
5575	P31321	5578	P17252	5595	P27361

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
6196	Q15349	6197	P51812	64130	Q9HAP6
7102	P41732	814	Q16566	815	Q9UQM7
9568	O75899				

5. Dopamine Neurotransmitter Release Cycle (R-HSA-212676)



Dopamine neurotransmitter cycle occurs in dopaminergic neurons. Dopamine is synthesized and loaded into the clathrin sculpted monoamine transport vesicles. The vesicles are docked, primed and fused with the plasmamembrane in the synapse to release dopamine into the synaptic cleft.

References

Westerink RH (2006). Targeting exocytosis: ins and outs of the modulation of quantal dopamine release. CNS Neurol Disord Drug Targets, 5, 57-77. [\[CrossRef\]](#)

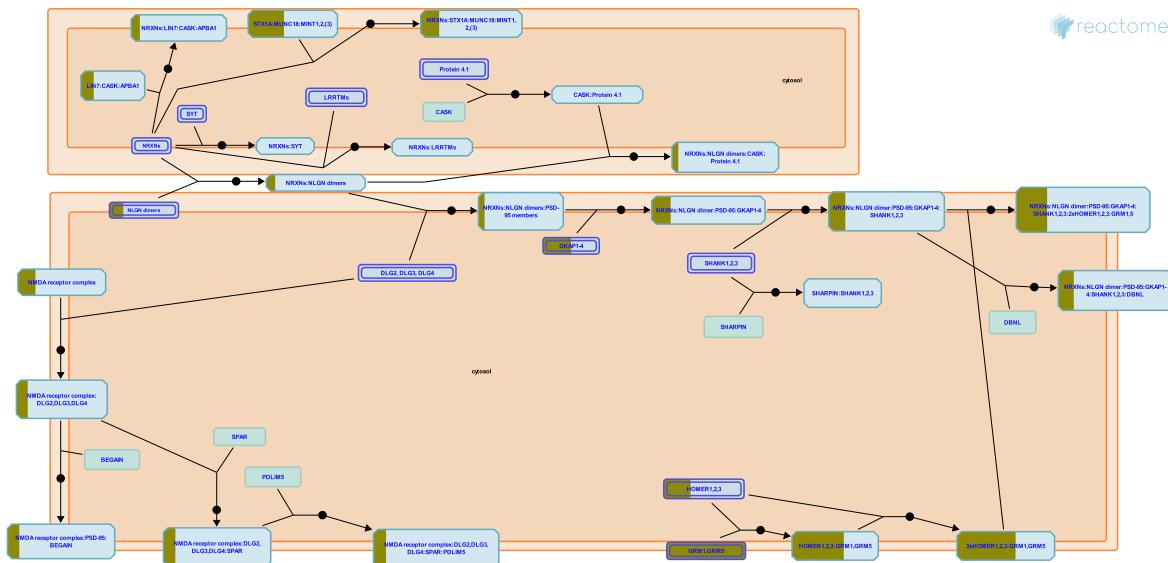
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Date	Action	Author
2008-01-14	Authored	Mahajan SS
2008-02-13	Created	Mahajan SS
2008-04-24	Reviewed	Kavalali E
2008-11-18	Edited	Mahajan SS
2021-09-10	Modified	Weiser JD

7 submitted entities found in this pathway, mapping to 7 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
3949	P63027	64130	Q9HAP6	6616	P60880
6804	Q16623	6854	Q92777	8500	Q13136
9256	O95153				

6. Neurexins and neuroligins (R-HSA-6794361)



Neurexins (NRXNs) and neuroligins (NLGNs) are best characterized synaptic cell-adhesion molecules. They are part of excitatory glutamatergic and inhibitory GABAergic synapses in mammalian brain, mediate trans-synaptic signaling, and shape neural network properties by specifying synaptic functions. As cell-adhesion molecules, NRXNs and NLGNs probably function by binding to each other and by interacting with intracellular PDZ-domain proteins, but the precise mechanisms involved and their relation to synaptic transmission remain unclear. The binding of NRXNs and NLGNs to their partners, helps to align the pre-synaptic release machinery and post-synaptic receptors. The importance of neurexins and neuroligins for synaptic function is evident from the dramatic deficits in synaptic transmission in mice lacking Nrxns or Nlgns. In humans, alterations in NRXNs or NLGNs genes are implicated in autism and other cognitive diseases, connecting synaptic cell adhesion to cognition and its disorders (Sudhof 2008, Craig et al. 2006, Craig & Kang 2007).

References

- Bang ML & Owczarek S (2013). A matter of balance: role of neurexin and neuroligin at the synapse. *Neurochem. Res.*, 38, 1174-89. [View](#)
- Papadopoulos T, Brose N, Tuffy LP & Krueger DD (2012). The role of neurexins and neuroligins in the formation, maturation, and function of vertebrate synapses. *Curr. Opin. Neurobiol.*, 22, 412-22. [View](#)
- Craig AM & Kang Y (2007). Neurexin-neuroligin signaling in synapse development. *Curr. Opin. Neurobiol.*, 17, 43-52. [View](#)
- Wright GJ & Washbourne P (2011). Neurexins, neuroligins and LRRTM5: synaptic adhesion getting fishy. *J. Neurochem.*, 117, 765-78. [View](#)
- McClelland AC, Dalva MB & Kayser MS (2007). Cell adhesion molecules: signalling functions at the synapse. *Nat. Rev. Neurosci.*, 8, 206-20. [View](#)

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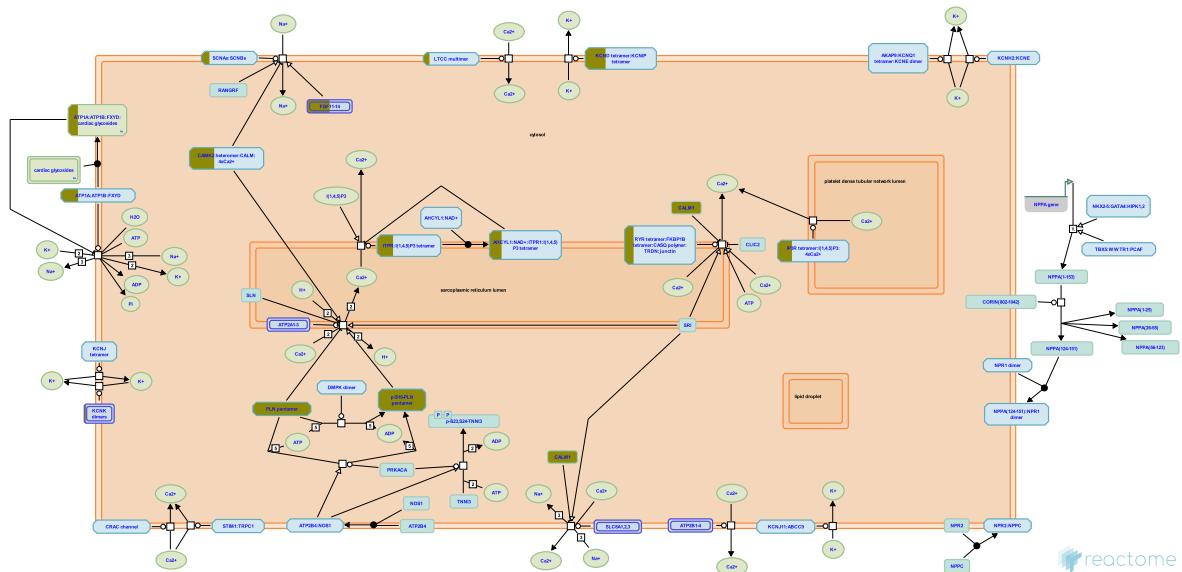
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Date	Action	Author
2015-09-04	Authored	Garapati P V
2015-09-04	Created	Garapati P V
2015-11-09	Reviewed	Washbourne P
2021-09-10	Modified	Weiser JD

10 submitted entities found in this pathway, mapping to 10 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
22829	Q8NFZ3	2739	Q14957	2742	Q13255
2915	P41594	321	Q99767	58512	O95886
64130	Q9HAP6	6804	Q16623	9228	Q9P1A6
9456	Q86YM7				

7. Cardiac conduction (R-HSA-5576891)



The normal sequence of contraction of atria and ventricles of the heart require activation of groups of cardiac cells. The mechanism must elicit rapid changes in heart rate and respond to changes in autonomic tone. The cardiac action potential controls these functions. Action potentials are generated by the movement of ions through transmembrane ion channels in cardiac cells. Like skeletal myocytes (and axons), in the resting state, a given cardiac myocyte has a negative membrane potential. In both muscle types, after a delay (the absolute refractory period), K⁺ channels reopen and the resulting flow of K⁺ out of the cell causes repolarisation. The voltage-gated Ca²⁺ channels on the cardiac sarcolemma membrane are generally triggered by an influx of Na⁺ during phase 0 of the action potential. Cardiac muscle cells are so tightly bound that when one of these cells is excited the action potential spreads to all of them. The standard model used to understand the cardiac action potential is the action potential of the ventricular myocyte (Park & Fishman 2011, Grant 2009).

The action potential has 5 phases (numbered 0-4). Phase 4 describes the membrane potential when a cell is not being stimulated. The normal resting potential in the ventricular myocardium is between -85 to -95 mV. The K⁺ gradient across the cell membrane is the key determinant in the normal resting potential. Phase 0 is the rapid depolarisation phase in which electrical stimulation of a cell opens the closed, fast Na⁺ channels, causing a large influx of Na⁺ creating a Na⁺ current (I_{Na⁺}). This causes depolarisation of the cell. The slope of phase 0 represents the maximum rate of potential change and differs in contractile and pacemaker cells. Phase 1 is the inactivation of the fast Na⁺ channels. The transient net outward current causing the small downward deflection (the "notch" of the action potential) is due to the movement of K⁺ and Cl⁻ ions. In pacemaker cells, this phase is due to rapid K⁺ efflux and closure of L-type Ca²⁺ channels. Phase 2 is the plateau phase which is sustained by a balance of Ca²⁺ influx and K⁺ efflux. This phase sustains muscle contraction. Phase 3 of the action potential is where a concerted action of two outward delayed currents brings about re-polarisation back down to the resting potential (Bartos et al. 2015).

References

Park DS & Fishman GI (2011). The cardiac conduction system. Circulation, 123, 904-15. ↗

Grandi E, Ripplinger CM & Bartos DC (2015). Ion Channels in the Heart. Compr Physiol, 5, 1423-64.



Grant AO (2009). Cardiac ion channels. Circ Arrhythm Electrophysiol, 2, 185-94. [🔗](#)

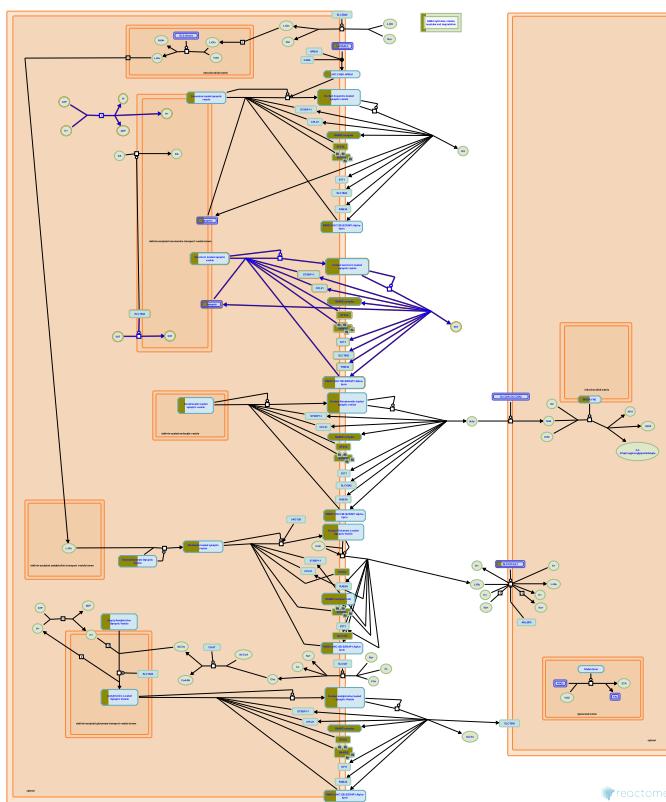
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Date	Action	Author
2014-05-27	Edited	Jassal B
2014-05-27	Authored	Jassal B
2014-05-27	Created	Jassal B
2015-11-09	Reviewed	Colotti G
2021-09-10	Modified	Weiser JD

17 submitted entities found in this pathway, mapping to 19 Reactome entities

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10089	Q9Y2U2	2167	P05023	2171	P14415
2258	P0DP23, Q92913	2259	P0DP23, Q92915	3708	Q14643
3751	Q9NZV8	3752	Q9UK17	476	P05023
478	P13637	5350	P26678	553	Q9NZV8
585	Q9Y5Y9	6329	P35499	747	P21817
782	Q02641	815	Q9UQM7		

8. Serotonin Neurotransmitter Release Cycle (R-HSA-181429)



reactome

Serotonin is synthesized in the serotonergic neurons in the central nervous system and the enterochromaffin cells of the gastrointestinal system. Serotonin is loaded into the clathrin sculpted monoamine transport vesicles. The vesicles are docked, primed and release after the change in the membrane potential that activates voltage gated calcium channels and the response by several proteins to the changes in intracellular Ca²⁺ increase leads to fusion of the vesicle and release of serotonin into the synapse.

References

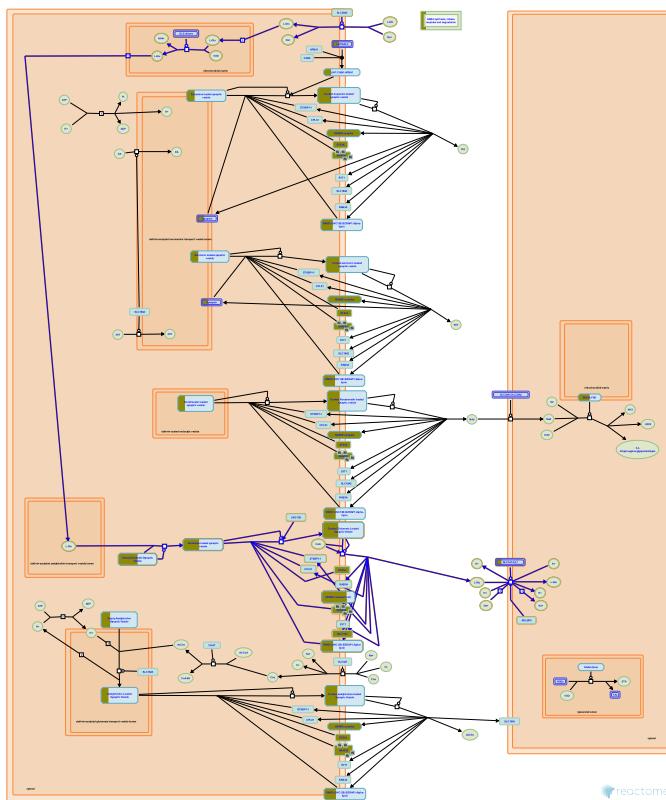
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Date	Action	Author
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2008-01-14	Authored	Mahajan SS
2008-04-24	Reviewed	Kavalali E
2008-11-18	Edited	Mahajan SS
2021-09-10	Modified	Weiser JD

6 submitted entities found in this pathway, mapping to 6 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
3949	P63027	6616	P60880	6804	Q16623
6854	Q92777	8500	Q13136	9256	O95153

9. Glutamate Neurotransmitter Release Cycle (R-HSA-210500)



Communication at the synapse involves the release of glutamate from the presynaptic neuron and its binding to glutamate receptors on the postsynaptic cell to generate a series of events that lead to propagation of the synaptic transmission. This process begins with the formation of synaptic vesicles in the presynaptic neuron, proceeds to the loading of glutamate into the vesicles, and concludes with the release of glutamate into the synaptic cleft.

The glutamate life cycle in the neuron begins with the loading of the nascent synaptic vesicles with cytosolic glutamate with the help the transporter protein, VGLUT1, located in the synaptic vesicular membrane. Glutamate loaded vesicles are formed in the cytoplasm and then transported to a site close to the plasma membrane where the vesicle is docked with the help of several proteins. One of the key players in the docking process is Munc 18, which interacts with syntaxin (in the plasma membrane), MINT (Munc18 interacting molecule), and DOC2. These interactions along with the secondary interactions are needed for docking the synaptic vesicle to the plasma membrane.

The docked synaptic vesicle is not ready for release until it undergoes molecular changes to prime it for fusion with the plasma membrane. Munc13 is one of the main players in the priming process. Munc 13 interacts with RIM (Rab3A interacting molecule) located in the synaptic vesicle. Munc 13 also interacts with DOC2. The precise molecular mechanisms of the interactions that result in docking versus priming are not clear and the docking and priming process have been combined in this annotation of this pathway. Once primed the synaptic vesicle is ready for release.

Synaptic transmission involves an action potential that is generated in the presynaptic cell which induces the opening of voltage gated Ca²⁺ channels (VGCC) located in the plasma membrane of the presynaptic neuron. Typically N, P/Q and R type of VGCCs are involved in the neurotransmitter release. Ca²⁺ influx through these channels results in the rise of intracellular Ca²⁺ concentration. In the microdomain of glutamatergic synapses, the Ca²⁺ concentration could rise between 10-25 micro molar. Synaptotagmin, a Ca²⁺-binding protein located in the synaptic vesicular membrane, responds to the rise in the Ca²⁺ levels in the microdomain and induces a synaptic vesicle membrane curvature that favors vesicle fusion. Fusion of the synaptic vesicle with the plasma membrane is characterized by the formation of a trimeric trans-SNARE complex that involves VAMP2 from the synaptic vesicle membrane, and syntaxin and SNAP-25 from plasma membrane. Vesicle fusion incorporates the synaptic vesicle membrane into the plasma membrane, releasing the vesicle contents (glutamate) into the synaptic cleft. Postfusion the synaptic vesicle membrane proteins (VAMP2, Rab3A, VGLUT1, and synaptotagmin) are also found in the plasma membrane.

References

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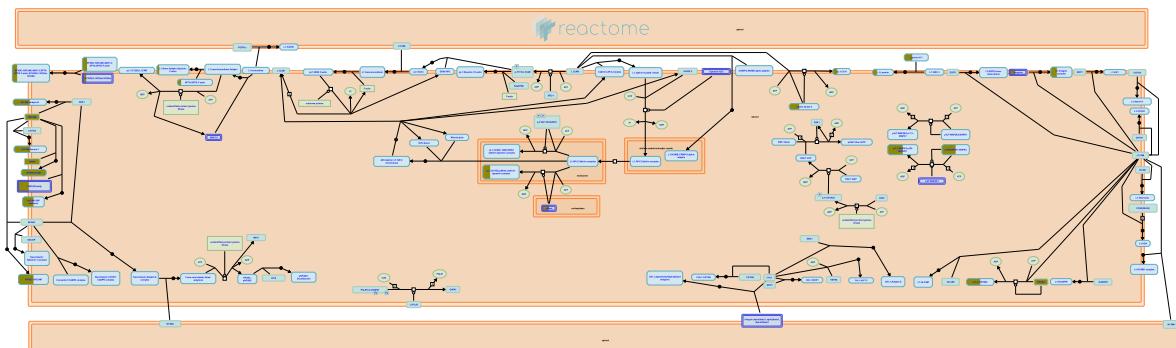
Edit history

Date	Action	Author
2008-01-14	Edited	Mahajan SS
2008-01-14	Authored	Mahajan SS
2008-01-14	Created	Mahajan SS
2008-04-24	Reviewed	Kavalali E
2021-09-10	Modified	Weiser JD

7 submitted entities found in this pathway, mapping to 7 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
1007	Q9P2U7	3949	P63027	6505	P43005
6616	P60880	6804	Q16623	8500	Q13136
9256	O95153				

10. L1CAM interactions (R-HSA-373760)



The L1 family of cell adhesion molecules (L1CAMs) are a subfamily of the immunoglobulin superfamily of transmembrane receptors, comprised of four structurally related proteins: L1, Close Homolog of L1 (CHL1), NrCAM, and Neurofascin. These CAMs contain six Ig like domains, five or six fibronectin like repeats, a transmembrane region and a cytoplasmic domain. The L1CAM family has been implicated in processes integral to nervous system development, including neurite outgrowth, neurite fasciculation and inter neuronal adhesion.

L1CAM members are predominately expressed by neuronal, as well as some nonneuronal cells, during development. Except CHL1 all the other members of L1 family contain an alternatively spliced 12-nucleotide exon, encoding the amino acid residues RSLE in the neuronal splice forms but missing in the non-neuronal cells. The extracellular regions of L1CAM members are divergent and differ in their abilities to interact with extracellular, heterophilic ligands. The L1 ligands include other Ig-domain CAMs (such as NCAM, TAG-1/axonin and F11), proteoglycans type molecules (neurocan), beta1 integrins, and extra cellular matrix protein laminin, Neuropilin-1, FGF and EGF receptors. Some of these L1-interacting proteins also bind to other L1CAM members. For example TAG-1/axonin interact with L1 and NrCAM; L1, neurofascin and CHL1 binds to contactin family members. The cytoplasmic domains of L1CAM members are most highly conserved. Nevertheless, they have different cytoplasmic binding partners, and even those with similar binding partners may be involved in different signaling complexes and mechanisms. The most conserved feature of L1CAMs is their ability to interact with the actin cytoskeletal adapter protein ankyrin. The cytoplasmic ankyrin-binding domain, exhibits the highest degree of amino acid conservation throughout the L1 family.

References

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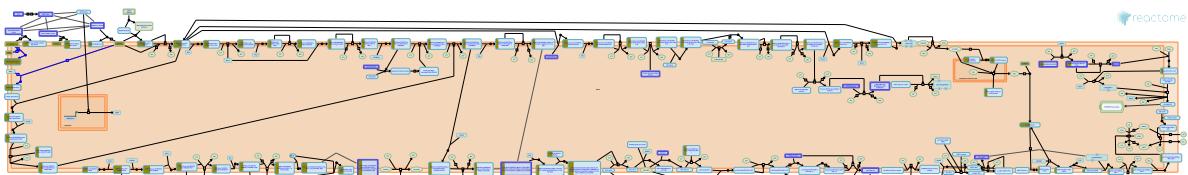
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Date	Action	Author
2008-07-16	Created	Garapati P V
2008-07-30	Edited	Garapati P V
2008-07-30	Authored	Garapati P V
2010-02-16	Reviewed	Maness PF
2021-09-10	Modified	Weiser JD

15 submitted entities found in this pathway, mapping to 15 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
1457	P68400	1524	O75676	1739	Q12959
2048	P29323	2444	P08648	26470	Q13797
284217	P25391	3751	O15020	4897	Q92823
5595	P27361	585	Q9Y5Y9	6196	Q15349
6197	P51812	6329	P35499	8828	O60462

11. Neuropilin interactions with VEGF and VEGFR (R-HSA-194306)



Cellular compartments: plasma membrane.

The plasma membrane-associated Neuropilin receptors NRP-1 and -2 bind some of the VEGF proteins and associate with VEGF receptor proteins. NRP-1 binds VEGF-A165, -B, and PLGF-2; NRP-2 also binds VEGF-A165 and PLGF-2, as well as VEGF-A145 and -C. The Neuropilin receptors appear to act as cofactors for the VEGF receptors, increasing their affinities for specific VEGF ligands, although the importance of this function *in vivo* remains unclear (Neufeld et al. 2002).

References

Herzog Y, Kessler O & Neufeld G (2002). The interaction of Neuropilin-1 and Neuropilin-2 with tyrosine-kinase receptors for VEGF. *Adv Exp Med Biol*, 515, 81-90. [View](#)

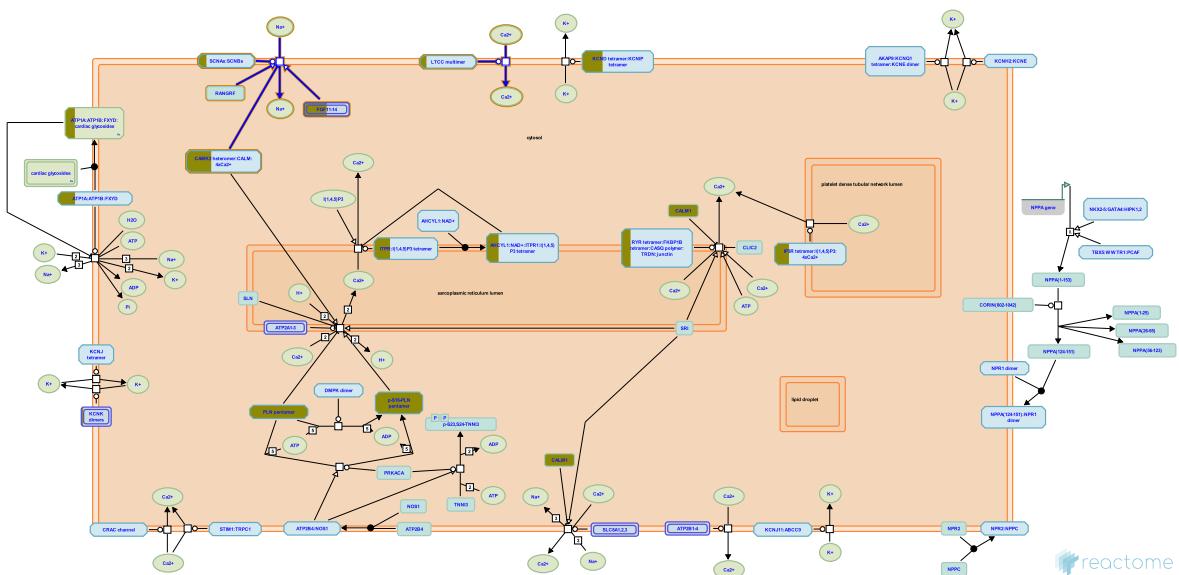
Edit history

Date	Action	Author
2007-03-12	Created	Gopinathrao G
2008-02-28	Reviewed	Claesson-Welsh L
2013-08-30	Edited	Garapati P V
2013-08-30	Authored	Garapati P V
2021-09-10	Modified	Weiser JD

3 submitted entities found in this pathway, mapping to 3 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
1812	P17948	1813	P35968	8828	O60462

12. Phase 0 - rapid depolarisation (R-HSA-5576892)



Phase 0 is the rapid depolarisation phase in which electrical stimulation of a cell initiates events involving the influx and efflux of ions resulting in the production of a cell's action potential. The cell's excitation opens the closed, fast Na^+ channel proteins, causing a large influx of Na^+ creating a Na^+ current (I_{Na^+}). This causes depolarisation of the cell then voltage-dependent L-type calcium channels (LTCCs) transport Ca^{2+} into excitable cells. The slope of phase 0 represents the maximum rate of potential change and differs in contractile and pacemaker cells. The potential in this phase changes from around -90mV to around +50mV (Park & Fishman 2011, Grant 2009).

References

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Grant AO (2009). Cardiac ion channels. Circ Arrhythm Electrophysiol, 2, 185-94. ↗

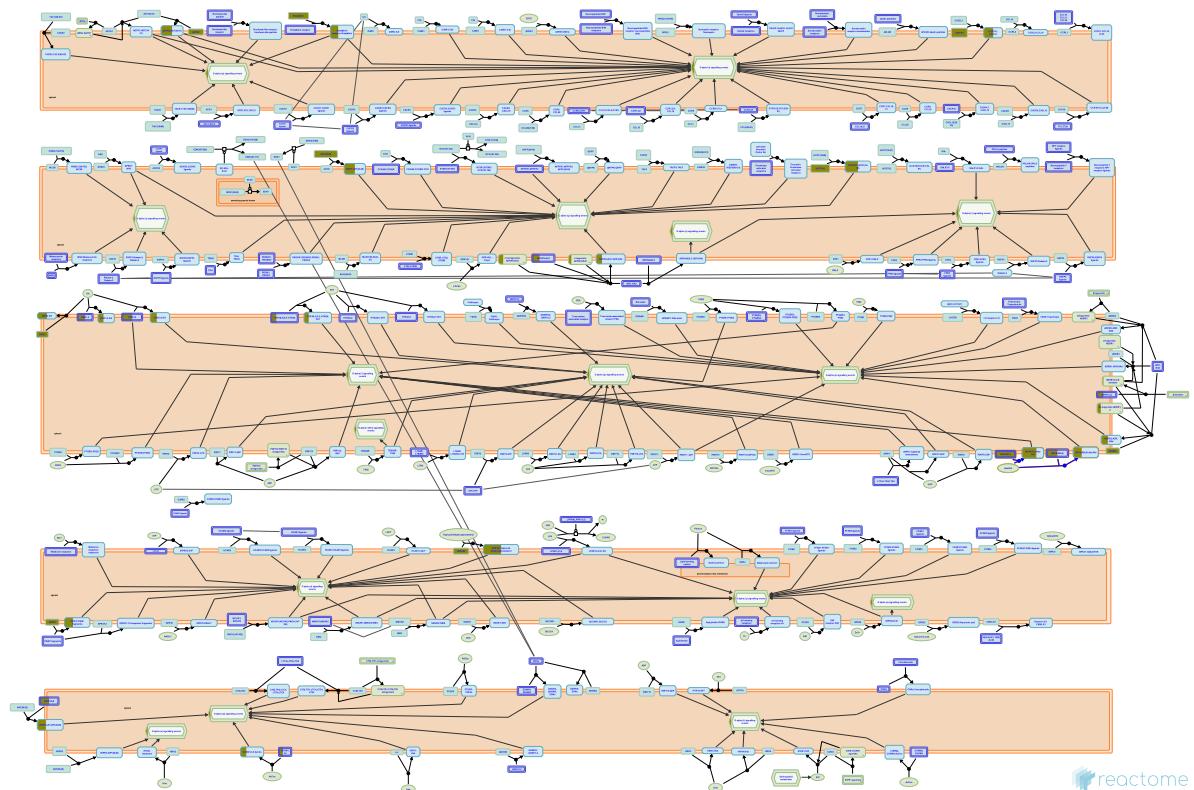
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Date	Action	Author
2014-05-27	Edited	Jassal B
2014-05-27	Authored	Jassal B
2014-05-27	Created	Jassal B
2015-11-09	Reviewed	Colotti G
2021-09-20	Modified	Weiser JD

6 submitted entities found in this pathway, mapping to 8 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
2258	P0DP23, Q92913	2259	P0DP23, Q92915	585	Q9Y5Y9
6329	P35499	782	Q02641	815	Q9UQM7

13. Adenosine P1 receptors (R-HSA-417973)



The adenosine receptors (P1 receptors) are a class of purinergic receptors, G-protein coupled receptors with adenosine as their endogenous ligand. In humans, there are four adenosine receptors. Each is encoded by a separate gene and the four receptors have distinct, though overlapping, functions. For instance, both A1 and A2A receptors play roles in the heart, regulating myocardial oxygen consumption and coronary blood flow. They also have important roles in the brain, regulating the release of other neurotransmitters such as dopamine and glutamate. The A2B and A3 receptors are located peripherally and are involved in processes such as inflammation and immune responses. (Fredholm BB et al, 2001).

References

Linden J, Fredholm BB, Jacobson KA, Klotz KN & IJzerman AP (2001). International Union of Pharmacology. XXV. Nomenclature and classification of adenosine receptors. *Pharmacol Rev*, 53, 527-52. ↗

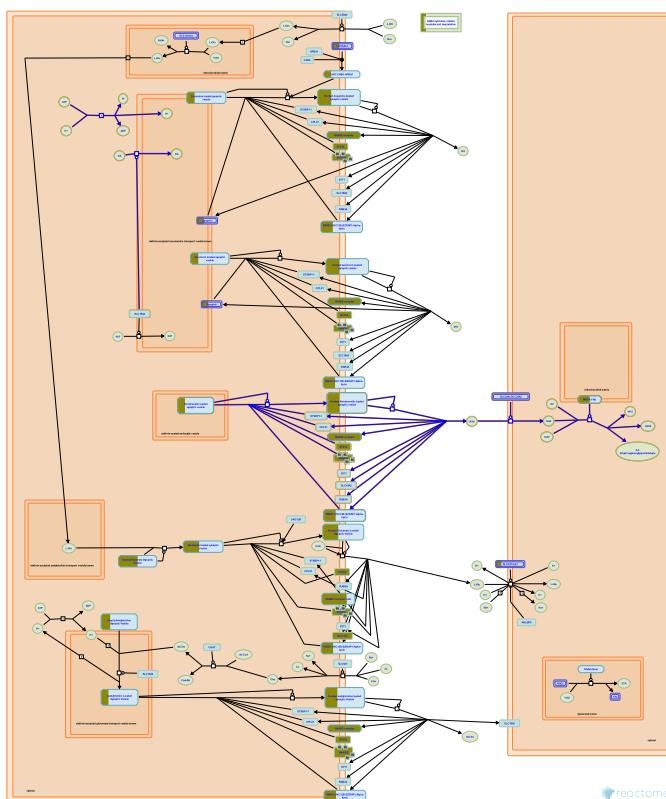
Edit history

Date	Action	Author
2009-04-14	Edited	Jassal B
2009-04-14	Authored	Jassal B
2009-04-14	Created	Jassal B
2009-05-29	Reviewed	D'Eustachio P
2021-09-10	Modified	Weiser JD

4 submitted entities found in this pathway, mapping to 4 Reactome entities

Input	UniProt Id	Input	UniProt Id
135	P29274	140	P0DMS8
18	P30542	2048	P30542

14. Norepinephrine Neurotransmitter Release Cycle (R-HSA-181430)



Noradrenalin release cycle consists of reacidification of the empty clathrin sculpted monoamine transport vesicle, loading of dopamine into reacidified clathrin coated monamine transport vesicle, conversion of dopamine into Noradrenalin, docking and priming of the noradrenalin synaptic vesicle and then release of noradrenalin synaptic vesicle. In the peripheral nervous system in the peripheral nervous system noradrenalin is stored in large and small dense vesicles and is released from large vesicles.

References

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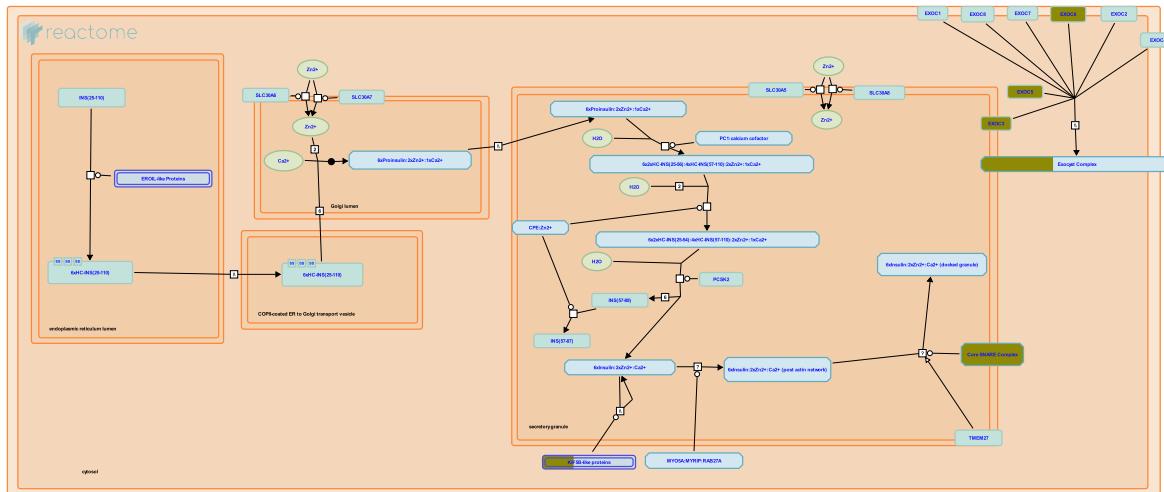
Date	Action	Author
2006-06-12	Created	Gillespie ME
2008-01-14	Authored	Mahajan SS
2008-11-18	Edited	Mahajan SS
2008-11-27	Reviewed	Restituito S

Date	Action	Author
2021-09-20	Modified	Weiser JD

6 submitted entities found in this pathway, mapping to 6 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
3949	P63027	4128	P21397	6616	P60880
6804	Q16623	8500	Q13136	9256	O95153

15. Insulin processing (R-HSA-264876)



Cellular compartments: secretory granule lumen, cytosol, endoplasmic reticulum lumen, COPII-coated ER to Golgi transport vesicle, extracellular region, Golgi lumen, nucleoplasm, plasma membrane, endoplasmic reticulum membrane, secretory granule membrane.

The generation of insulin-containing secretory granules from proinsulin in the lumen of the endoplasmic reticulum (ER) can be described in 4 steps: formation of intramolecular disulfide bonds, formation of proinsulin-zinc-calcium complexes, proteolytic cleavage of proinsulin to yield insulin, translocation of the granules across the cytosol to the plasma membrane.

Transcription of the human insulin gene INS is activated by 4 important transcription factors: Pdx-1, MafA, Beta2/NeuroD1, and E47. The transcription factors interact with each other at the promoters of the insulin gene and act synergistically to promote transcription. Expression of the transcription factors is upregulated in response to glucose.

The preproinsulin mRNA is translated by ribosomes at the rough endoplasmic reticulum (ER) and the preproinsulin enters the secretion pathway by virtue of its signal peptide, which is cleaved during translation to yield proinsulin. Evidence indicates that the preproinsulin mRNA is stabilized by glucose.

In the process annotated in detail here, within the ER, three intramolecular disulfide bonds form between cysteine residues in the proinsulin. Formation of the bonds is the spontaneous result of the conformation of proinsulin and the oxidizing environment of the ER, which is maintained by Ero1-like alpha

The cystine bonded proinsulin then moves via vesicles from the ER to the Golgi Complex. High concentrations of zinc are maintained in the Golgi by zinc transporters ZnT5, ZnT6, and ZnT7 and the proinsulin forms complexes with zinc and calcium.

Proinsulin-zinc-calcium complexes bud in vesicles from the trans-Golgi to form immature secretory vesicles (secretory granules) in the cytosol. Within the immature granules the endoproteases Prohormone Convertase 1/3 and Prohormone Convertase 2 cleave at two sites of the proinsulin and Carboxypeptidase E removes a further 4 amino acid residues to yield the cystine-bonded A and B chains of mature insulin and the C peptide, which will also be secreted with the insulin. The insulin-zinc-calcium complexes form insoluble crystals within the granule

The insulin-containing secretory granules are then translocated across the cytosol to the inner surface of the plasma membrane. Translocation occurs initially by attachment of the granules to Kinesin-1, which motors along microtubules, and then by attachment to Myosin Va, which motors along the microfilaments of the cortical actin network.

A pancreatic beta cell contains about 10000 insulin granules of which about 1000 are docked at the plasma membrane and 50 are readily releasable in immediate response to stimulation by glucose or other secretagogues. Docking is due to interaction between the Exocyst proteins EXOC3 on the granule membrane and EXOC4 on the plasma membrane. Exocytosis is accomplished by interaction between SNARE-type proteins Syntaxin 1A and Syntaxin 4 on the plasma membrane and Synaptobrevin-2/VAMP2 on the granule membrane. Exocytosis is a calcium-dependent process due to interaction of the calcium-binding membrane protein Synaptotagmin V/IX with the SNARE-type proteins.

References

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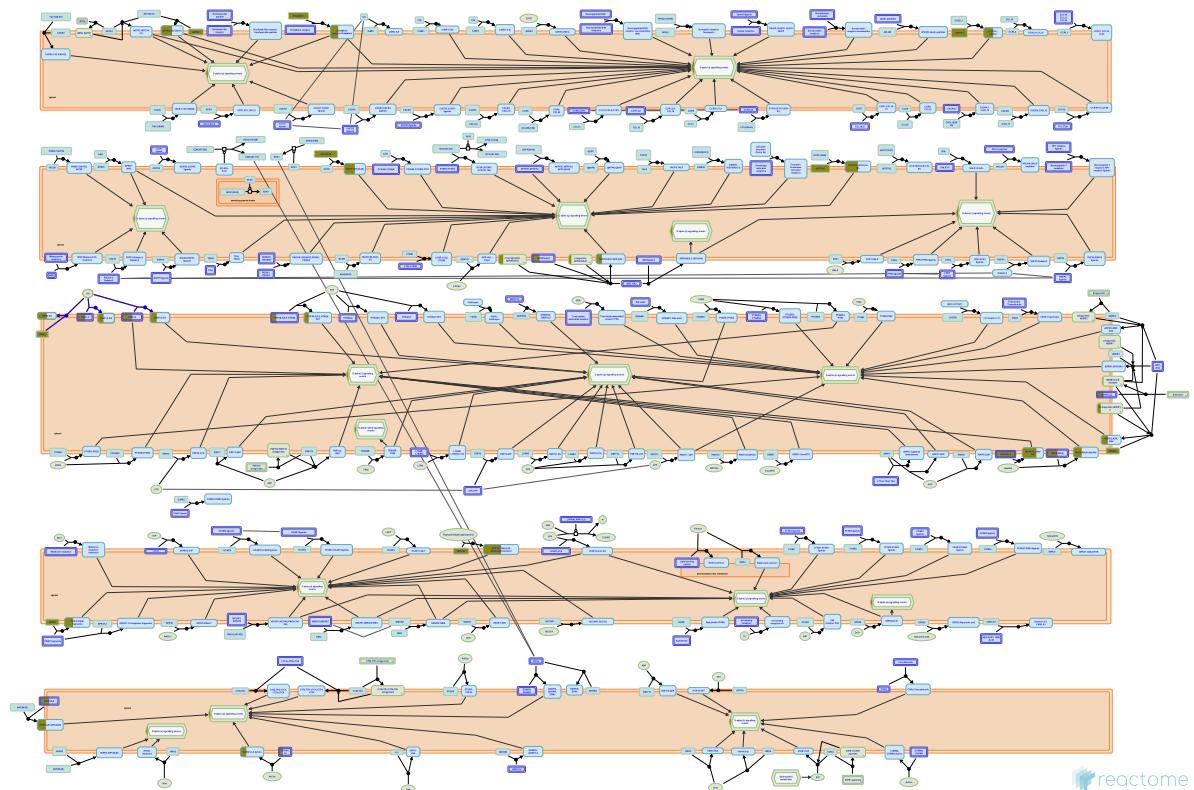
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Date	Action	Author
2008-04-15	Created	May B
2008-11-20	Edited	May B, Gopinathrao G
2008-11-20	Authored	May B, Gopinathrao G
2008-12-02	Reviewed	Matthews L, Gillespie ME, D'Eustachio P
2021-09-10	Modified	Weiser JD

6 submitted entities found in this pathway, mapping to 6 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
10640	O00471	11336	O60645	3800	O60282
3949	P63027	54536	Q8TAG9	6804	Q16623

16. Dopamine receptors (R-HSA-390651)



Dopamine receptors play vital roles in processes such as the control of learning, motivation, fine motor control and modulation of neuroendocrine signaling (Girault JA and Greengard P, 2004). Abnormalities in dopamine receptor signaling may lead to neuropsychiatric disorders such as Parkinson's disease and schizophrenia. Dopamine receptors are prominent in the CNS and the neurotransmitter dopamine is the primary endogenous ligand for these receptors. In humans, there are five distinct types of dopamine receptor, D1-D5. They are subdivided into two families; D1-like family (D1 and D5) which couple with the G protein alpha-s and are excitatory and D2-like family (D2,D3 and D4) which couple with the G protein alpha-i and are inhibitory (Kebabian JW and Calne DB, 1979).

References

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Kebabian JW & Calne DB (1979). Multiple receptors for dopamine. *Nature*, 277, 93-6.



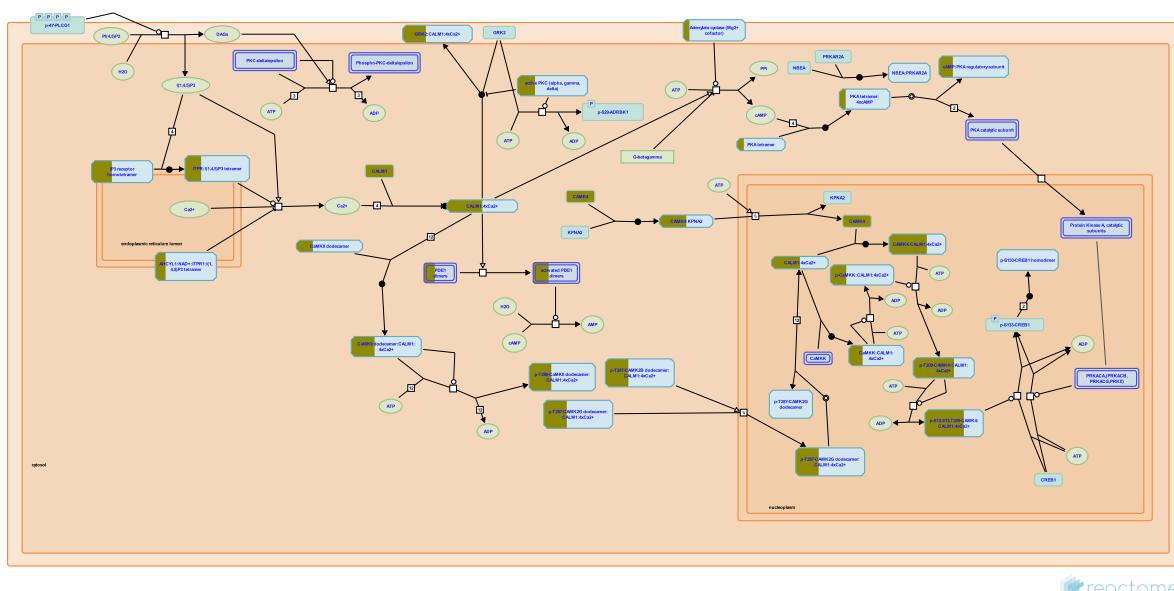
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Date	Action	Author
2009-02-10	Edited	Jassal B
2009-02-10	Authored	Jassal B
2009-02-10	Created	Jassal B
2009-03-02	Reviewed	D'Eustachio P
2021-09-10	Modified	Weiser JD

3 submitted entities found in this pathway, mapping to 3 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
1812	P21728	1813	P14416	1814	P35462

17. DAG and IP3 signaling (R-HSA-1489509)



Cellular compartments: plasma membrane, extracellular region, cytosol.

This pathway describes the generation of DAG and IP₃ by the PLCgamma-mediated hydrolysis of PIP₂ and the subsequent downstream signaling events.

References

Snyder SH, Nikolaidis N, van Rossum DB, Gill DL & Patterson RL (2005). Phospholipase C-gamma: diverse roles in receptor-mediated calcium signaling. Trends Biochem Sci, 30, 688-97. 

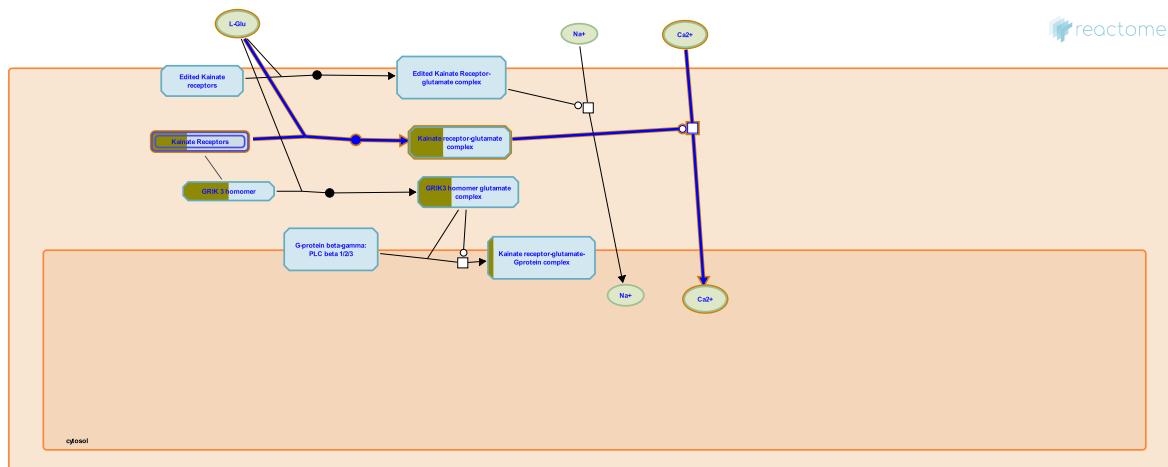
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Date	Action	Author
2006-10-10	Authored	Annibali D, Nasi S
2007-11-08	Reviewed	Greene LA
2011-08-15	Created	Rothfels K
2021-09-20	Modified	Weiser JD

9 submitted entities found in this pathway, mapping to 9 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
111	O95622	2258	P0DP23	2259	P0DP23
3708	Q14643	5137	Q14123	5575	P31321
5578	P17252	814	Q16566	815	Q9UQM7

18. Activation of Ca-permeable Kainate Receptor (R-HSA-451308)



Cellular compartments: plasma membrane, extracellular region, cytosol.

Kainate receptors that are assembled with subunits GRIK1-5, are Ca^{2+} permeable if GRIK1 and GRIK2 are not edited at the Q/R or other sites.

These channels permit Ca^{2+} upon activation by glutamate or other agonists.

References

Lees GJ (2000). Pharmacology of AMPA/kainate receptor ligands and their therapeutic potential in neurological and psychiatric disorders. Drugs, 59, 33-78. [\[link\]](#)

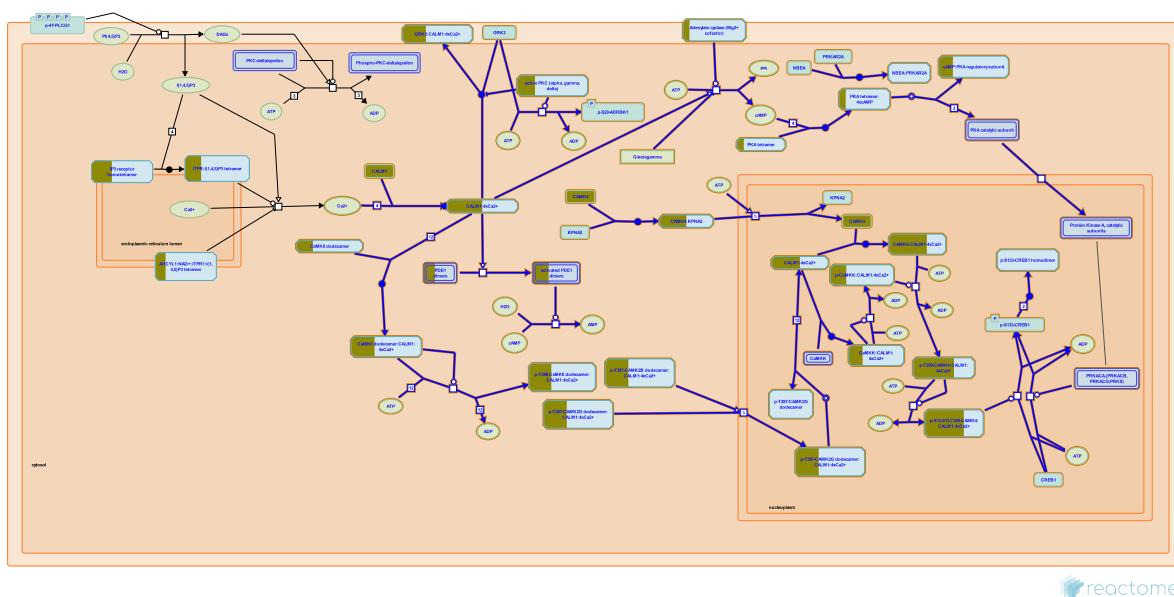
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Date	Action	Author
2009-11-18	Reviewed	Tukey D
2010-01-05	Created	Mahajan SS
2010-01-15	Authored	Mahajan SS
2010-02-06	Edited	Gillespie ME
2021-09-20	Modified	Weiser JD

5 submitted entities found in this pathway, mapping to 5 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
1739	Q12959	2258	P0DP23	2259	P0DP23
2899	Q13003	2900	Q16099		

19. CaM pathway (R-HSA-111997)



Cellular compartments: nucleoplasm, plasma membrane, cytosol.

Calmodulin (CaM) is a small acidic protein that contains four EF-hand motifs, each of which can bind a calcium ion, therefore it can bind up to four calcium ions. The protein has two approximately symmetrical domains, separated by a flexible hinge region. Calmodulin is the prototypical example of the EF-hand family of Ca²⁺-sensing proteins. Changes in intracellular Ca²⁺ concentration regulate calmodulin in three distinct ways. First, by directing its subcellular distribution. Second, by promoting association with different target proteins. Third, by directing a variety of conformational states in calmodulin that result in target-specific activation. Calmodulin binds and activates several effector protein (e.g. the CaM-dependent adenylyl cyclases, phosphodiesterases, protein kinases and the protein phosphatase calcineurin).

References

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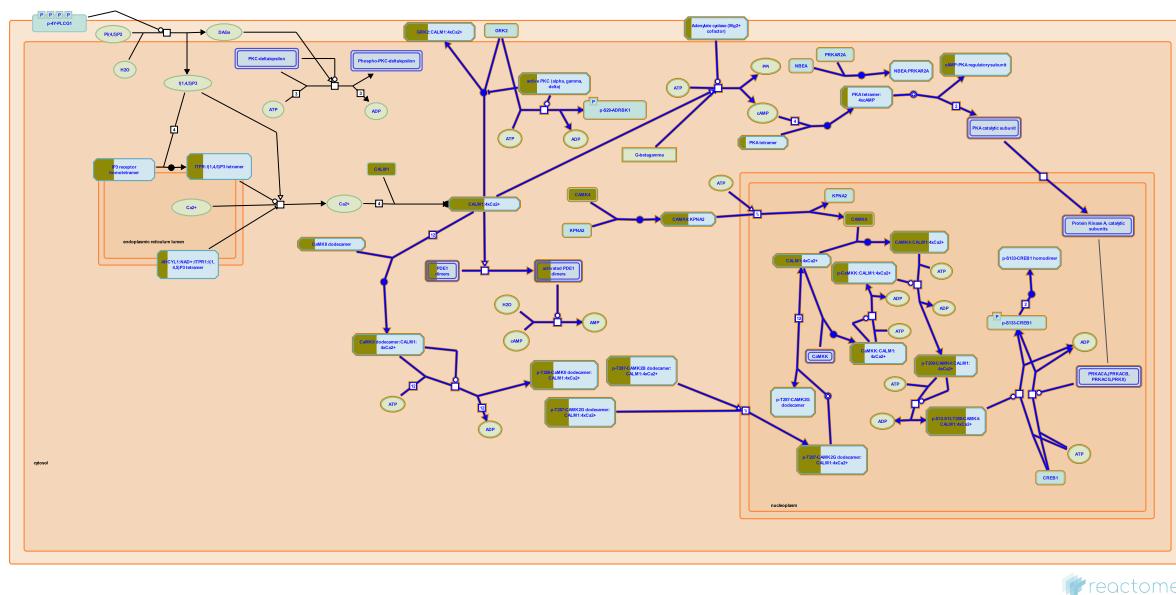
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Date	Action	Author
2004-03-31	Authored	Jassal B, Le Novere N
2004-03-31	Created	Schmidt EE
2008-11-06	Edited	Jassal B
2008-11-06	Reviewed	Castagnoli L
2021-09-20	Modified	Weiser JD

8 submitted entities found in this pathway, mapping to 8 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
111	O95622	2258	P0DP23	2259	P0DP23
5137	Q14123	5575	P31321	5578	P17252
814	Q16566	815	Q9UQM7		

20. Calmodulin induced events (R-HSA-111933)



Cellular compartments: nucleoplasm, plasma membrane, cytosol.

One important physiological role for Calmodulin is the regulation of adenylyl cyclases. Four of the nine known adenylyl cyclases are calcium sensitive, in particular type 8 (AC8).

References

Storm DR & Ferguson GD (2004). Why calcium-stimulated adenylyl cyclases?. Physiology (Bethesda) , 19, 271-6. [\[CrossRef\]](#)

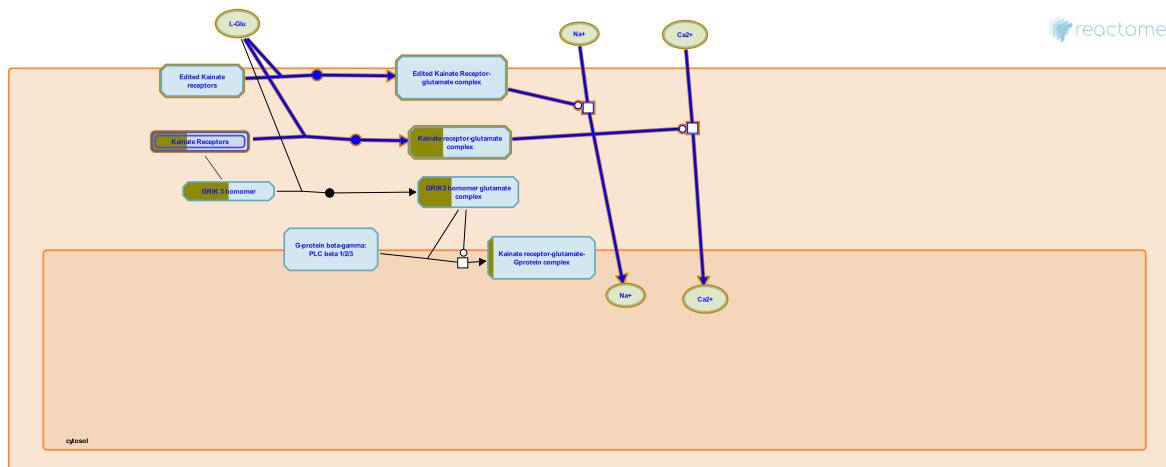
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2004-03-25	Created	Schmidt EE
2004-03-31	Authored	Jassal B, Le Novere N
2008-11-06	Edited	Jassal B
2008-11-06	Reviewed	Castagnoli L
2021-09-20	Modified	Weiser JD

8 submitted entities found in this pathway, mapping to 8 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
111	O95622	2258	P0DP23	2259	P0DP23
5137	Q14123	5575	P31321	5578	P17252
814	Q16566	815	Q9UQM7		

21. Ionotropic activity of kainate receptors (R-HSA-451306)



Cellular compartments: plasma membrane, extracellular region, cytosol.

Kainate receptors are either Ca²⁺ permeable or impermeable depending on the composition of the receptor and the editing status of subunits GluR5 and GluR6 (GRIK1 and 2).

References

Mulle C & Pinheiro P (2006). Kainate receptors. *Cell Tissue Res*, 326, 457-82. [View](#)

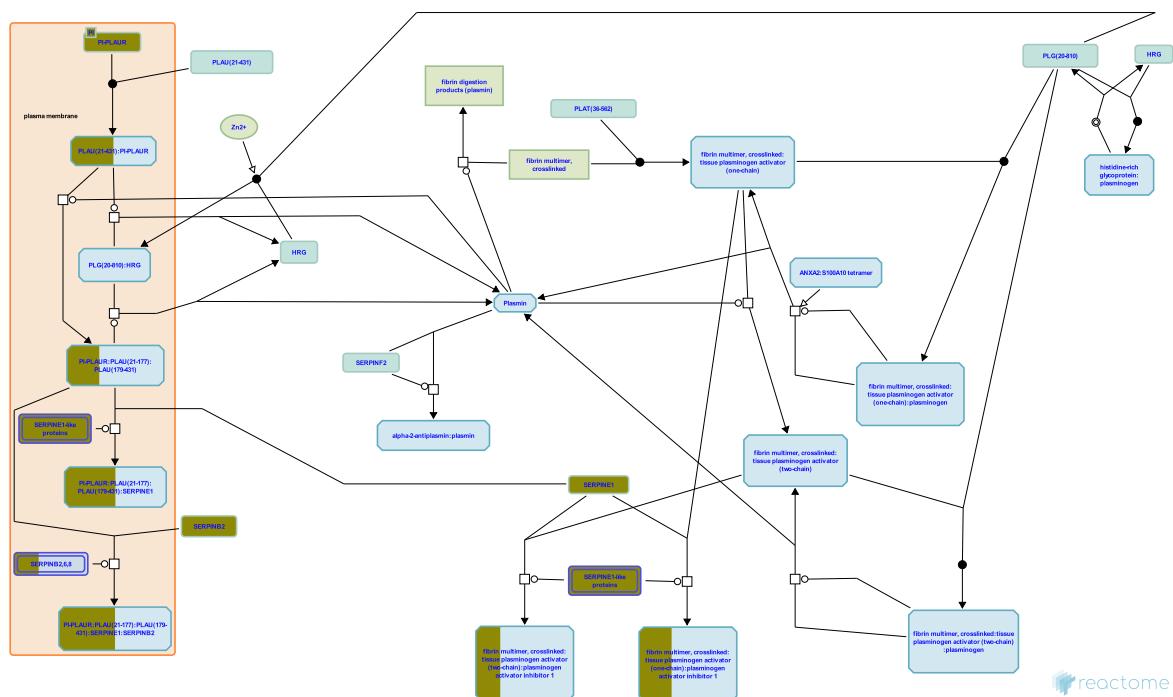
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Date	Action	Author
2009-11-18	Reviewed	Tukey D
2010-01-05	Created	Mahajan SS
2010-01-15	Authored	Mahajan SS
2010-02-06	Edited	Gillespie ME
2021-09-10	Modified	Weiser JD

5 submitted entities found in this pathway, mapping to 5 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
1739	Q12959	2258	P0DP23	2259	P0DP23
2899	Q13003	2900	Q16099		

22. Dissolution of Fibrin Clot (R-HSA-75205)



The crosslinked fibrin multimers in a clot are broken down to soluble polypeptides by plasmin, a serine protease. Plasmin can be generated from its inactive precursor plasminogen and recruited to the site of a fibrin clot in two ways, by interaction with tissue plasminogen activator at the surface of a fibrin clot, and by interaction with urokinase plasminogen activator at a cell surface. The first mechanism appears to be the major one responsible for the dissolution of clots within blood vessels. The second, although capable of mediating clot dissolution, may normally play a major role in tissue remodeling, cell migration, and inflammation (Chapman 1997; Lijnen 2001).

Clot dissolution is regulated in two ways. First, efficient plasmin activation and fibrinolysis occur only in complexes formed at the clot surface or on a cell membrane - proteins free in the blood are inefficient catalysts and are rapidly inactivated. Second, both plasminogen activators and plasmin itself are inactivated by specific serpins, proteins that bind to serine proteases to form stable, enzymatically inactive complexes (Kohler and Grant 2000).

These events are outlined in the drawing: black arrows connect the substrates (inputs) and products (outputs) of individual reactions, and blue lines connect output activated enzymes to the other reactions that they catalyze.

References

- Lijnen HR (2001). Elements of the fibrinolytic system. Ann N Y Acad Sci, 936, 226-36. [🔗](#)
- Kohler HP & Grant PJ (2000). Plasminogen-activator inhibitor type 1 and coronary artery disease. N Engl J Med, 342, 1792-801. [🔗](#)
- Chapman HA (1997). Plasminogen activators, integrins, and the coordinated regulation of cell adhesion and migration. Curr Opin Cell Biol, 9, 714-24. [🔗](#)

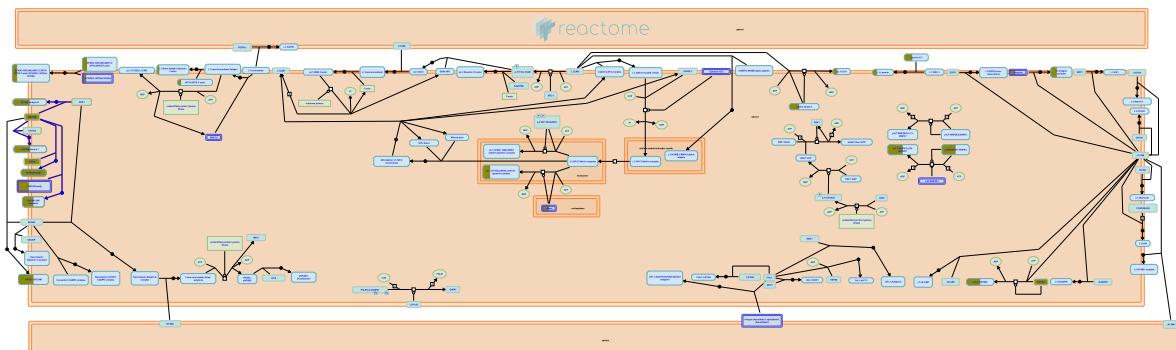
Edit history

Date	Action	Author
2008-01-11	Reviewed	Rush MG
2021-08-26	Edited	D'Eustachio P
2021-09-10	Modified	Weiser JD

4 submitted entities found in this pathway, mapping to 4 Reactome entities

Input	UniProt Id	Input	UniProt Id
5054	P05121	5329	Q03405
56144	P07093	92737	P05120

23. NrCAM interactions (R-HSA-447038)



Cellular compartments: plasma membrane.

The NgCAM-related cell adhesion molecule (NrCAM) is member of the L1 family involved in the eye development and node of Ranvier. Like all the other members of L1 family NrCAM also has the ability to bind to ankyrins. The last C-terminal amino acids of NrCAM form a PDZ-binding motif and can interact with SAP (synapse-associated protein) 102 and SAP97. Member of the GPI-anchored TAG-1/axonin-1 have been shown to interact with NrCAM. NrCAM also binds the Sema3B receptor NP-2 to mediate repulsive axon guidance.

References

- Castellani V, Grumet M, Sanes JR, Hoyo-Becerra C, Bozon M, Nawabi H, ... Püschel AW (2005). Dual functional activity of semaphorin 3B is required for positioning the anterior commissure. *Neuron*, 48, 63-75. [🔗](#)
- Hortsch M (2000). Structural and functional evolution of the L1 family: are four adhesion molecules better than one?. *Mol Cell Neurosci*, 15, 1-10. [🔗](#)
- Gunn-Moore FJ, Hill M, Herron LR & Davey F (2009). The intracellular interactions of the L1 family of cell adhesion molecules. *Biochem J*, 419, 519-31. [🔗](#)

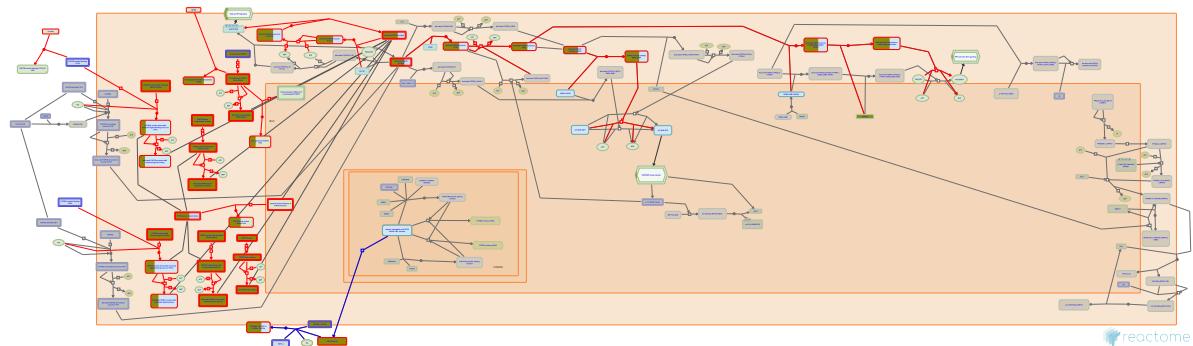
Edit history

Date	Action	Author
2008-07-30	Edited	Garapati P V
2008-07-30	Authored	Garapati P V
2009-11-19	Created	Garapati P V
2010-02-16	Reviewed	Maness PF
2010-05-19	Modified	Garapati P V

3 submitted entities found in this pathway, mapping to 3 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
1739	Q12959	4897	Q92823	8828	O60462

24. Signaling by FGFR2 IIIa TM (R-HSA-8851708)



Diseases: acrocephalosyndactylia.

A soluble truncated form of FGFR2 is aberrantly expressed in an Apert Syndrome mouse model and inhibits FGFR signaling in vitro and in vivo. This variant, termed FGFR IIIa TM, arises from a mis-spliced transcript that fuses exon 7 to exon 10 and that escapes nonsense-mediated decay. FGFR2 IIIa TM may inhibit signaling by sequestering FGF ligand and/or by forming nonfunctional heterodimers with full-length receptors at the cell surface (Wheldon et al, 2011).

References

Hajihosseini MK, Khodabukus N, Heath JK, Smith TG, Patey SJ & Wheldon LM (2011). Identification and characterization of an inhibitory fibroblast growth factor receptor 2 (FGFR2) molecule, up-regulated in an Apert Syndrome mouse model. Biochem. J., 436, 71-81. [View](#)

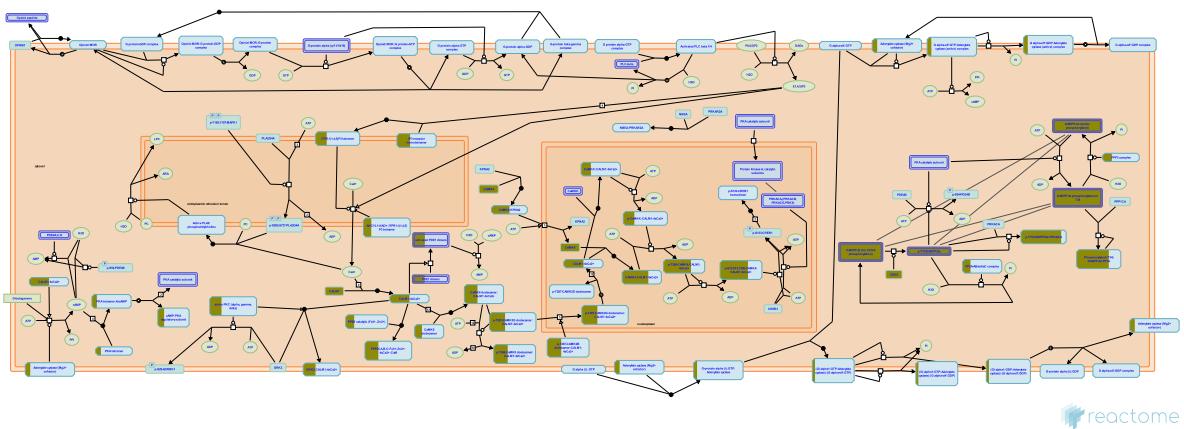
Edit history

Date	Action	Author
2016-01-09	Edited	Rothfels K
2016-01-09	Authored	Rothfels K
2016-01-09	Created	Rothfels K
2016-01-25	Modified	Rothfels K
2016-01-25	Reviewed	Grose RP

1 submitted entities found in this pathway, mapping to 5 Reactome entities

Input	UniProt Id
1809	P21802, P21802-1, P21802-18, P21802-3, P21802-5

25. Opioid Signalling (R-HSA-111885)



Opioids are chemical substances similar to opiates, the active substances found in opium (morphine, codeine etc.). Opioid action is mediated by the receptors for endogenous opioids; peptides such as the enkephalins, the endorphins or the dynorphins. Opioids possess powerful analgesic and sedative effects, and are widely used as pain-killers. Their main side-effect is the rapid establishment of a strong addiction. Opioids receptors are G-protein coupled receptors (GPCR). There are four classes of receptors: mu (MOR), kappa (KOR) and delta (DOR), and the nociceptin receptor (NOP).

References

- Gabrilovac J, Balog T & Martin-Kleiner I (2006). Signal transduction induced by opioids in immune cells: a review. *Neuroimmunomodulation*, 13, 1-7. [🔗](#)
- Pasternak GW & Standifer KM (1997). G proteins and opioid receptor-mediated signalling. *Cell Signal*, 9, 237-48. [🔗](#)
- Hamm HE (1998). The many faces of G protein signaling. *J Biol Chem*, 273, 669-72. [🔗](#)

Edit history

Date	Action	Author
2004-03-24	Created	Schmidt EE
2004-03-31	Authored	Jassal B, Le Novere N
2008-11-06	Reviewed	Castagnoli L
2021-08-26	Edited	Schmidt EE
2021-09-10	Modified	Weiser JD

13 submitted entities found in this pathway, mapping to 13 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
111	O95622	1977	Q00535	2258	P0DP23
2259	P0DP23	3708	Q14643	5137	Q14123
5519	P30154	5530	Q08209	5575	P31321
5578	P17252	814	Q16566	815	Q9UQM7
84152	Q9UD71				

6. Identifiers found

Below is a list of the input identifiers that have been found or mapped to an equivalent element in Reactome, classified by resource.

381 of the submitted entities were found, mapping to 491 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
1006	P55286	1007	Q9P2U7	10071	Q9UKN1
1008	Q9Y6N8	10082	Q9Y625	10089	Q9Y2U2
1009	P55287	10207	Q8NI35	10288	Q8N423
10347	Q8IZY2	10349	Q8WWZ4	10482	Q9UBU9
10585	Q9Y6A1	10640	O00471	10999	Q6P1M0
1105	O14646	11059	Q9H0M0	11069	Q8WZA2
111	O95622	11103	Q13601	11128	O14802
11141	Q9NZN1	1131	P20309	11336	O60645
1142	Q05901	114785	Q96DN6	114791	Q96RT8
114805	Q8IUC8	116442	Q96DA2	1183	P51793
123606	Q7RTP0	128239	Q86VI3	132	P55263
135	P29274	1376	P35354	137970	Q6UXZ4
140	P0DMS8	142686	A6NK59	1454	P49674
1457	P68400	147694	Q8NEK5	147968	Q6ZSI9
1524	O75676	154	P07550	154664	Q86UQ4
1584	P42785	159	P30520	161357	Q7Z553
1636	P12821	1644	P20711	170572	Q8WXA8
1739	Q12959	1746	Q9GZZ7	1750	P56179
1762	Q9Y239	1793	Q14185	18	P80404
1803	P16234	1804	P09619	1806	P07333
1809	P21802, P21802-1, P21802-18, P21802-3, P21802-5	1812	P17948	1813	P35968
1814	P35462	1857	Q92997	186	P50052
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1977	Q00535	1981	Q04637	1993	Q12926
199777	Q68DY1	2020	O75460	202559	Q5VWX1
2048	P29323	2055	P35348	2078	Q99759
2100	Q92731	2103	O95718	2131	Q5VST9
2167	P05023	2171	P14415	2195	P54687
221037	Q15652	221656	Q8NB78	222537	Q8IZT8
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23380	O75044	23451	O75533	23476	O60885
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23649	Q14181	23705	Q9BY67	2395	Q16595
2444	P08648	253559	Q8N3J6	253980	Q8WZ19
2547	P50120	2557	P48169	257194	Q7Z3B1
25769	Q96T83	25913	Q9NUX5	26019	Q9HAU5

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
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2739	Q14957	2742	P23416, Q13255	2778	P63092, Q5JWF2
2820	O43566	28234	Q9NPD5	284217	P25391
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2899	Q13003	2900	Q16099	2915	P41594
2917	Q14831	2944	P09488	2969	Q6IA17
2977	P33402	29781	Q6IBW4	30010	Q96D96
3105	P04439	3106	P29372	3115	P04440
3123	P01911	3135	P17693	321	Q99767
3290	Q9UM07	3351	P28222	3359	P46098
340267	Q2UY09	340385	Q6ZMY9	342132	Q6NX45
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3628	P49441	367	P47901	3708	Q14643
3746	P48547	3751	Q9NZV8	3752	Q9UK17
375775	Q6ZV29	3772	Q99712	3778	Q12791
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394	Q13017	3949	P63027	3952	P41159
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4137	P10636-8	4152	Q9UIS9	4173	P33991
4175	Q14566	4241	P08582	4359	P25189
438	P78508	440193	Q9P219	4481	P21757
4482	Q9UJ68	4488	P35548	4524	P42898
4585	Q99102	4638	Q15746	4698	Q16718
4756	Q92859	476	Q07001	4774	Q12857
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4862	Q99743	4897	Q92823	4914	P04629, P04629-1
4916	Q16288	5020	P01178	5049	P68402
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5530	Q08209	55356	Q8IZD6	55558	P51805
55689	Q9ULM3	55746	Q8WUM0	5575	P31321
5578	P17252	5591	P78527	5595	P27361
56135	P15882	56138	Q6ZP29	56141	P61513
56143	Q9Y624	56144	P07093	56145	Q9BZX2
56147	Q9BZV2	56160	Q96MG7	563	P56696
57154	Q9HCE7	57282	Q6U841	5743	P35354
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Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
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65267	Q9BYP7	6532	P31645	6535	P48029
6616	P60880	6624	Q16658	6647	P00441
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675	P59534	6804	Q16623	683	Q10588
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7471	P04628	7514	O14980	7531	P62258
7532	P61981	7566	P17022	765	Q8WWZ4
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781	O15438	782	Q02641	7837	Q92626
7850	P27930	79623	Q96FL9	79648	Q8NEM0
80184	O15078	80204	Q86XK2	81	P32249
814	Q16566	815	Q9UQM7	81614	Q8N8Q9
81887	Q9Y4W2	8218	P53675	8295	Q9Y4A5
83692	Q8TCZ2	83852	Q96T68	84152	Q9UD71
84282	Q8IUD6	84433	Q9BXL7	84527	Q9BR84
8481	O75665	84812	Q9BRC7	84871	Q5VU57
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8604	O75746	881	Q6PXP3	8828	O60462
8867	O43426	8911	Q9P0X4	8913	O43497
8930	O95243	8945	Q9Y297	8970	P06899
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9568	O75899	9572	P20393	9639	O15013
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Input	ChEBI Id	Input	ChEBI Id	Input	ChEBI Id
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7. Identifiers not found

These 133 identifiers were not found neither mapped to any entity in Reactome.

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343413	344148	344558	392862	401145	4139	4288	4335
4622	4643	5013	5047	50945	5101	51629	5307
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56139	56140	56142	56146	56899	57471	57496	57575
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7982	80194	80381	80737	80790	8287	83481	83538
83593	83855	83943	84056	84326	84332	84445	84465
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