INGENUITY PATHWAY ANALYSIS

Canonical Pathway

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Canonical Pathway: ## Synaptogenesis Signaling Pathway

Description: The chemical synapse represents a specialized functional and morphological cell structure where a presynaptic neuron communicates with the postsynaptic cell. Synaptic junctions are composed of three compartments: the presynaptic bouton, the synaptic cleft and the postsynaptic reception apparatus. These cell-cell contacts take about 1-2 hours to form, and are mediated by extracellular interactions between a variety of adhesion proteins including neuroligins, neurexin, cadherins, ephrin, SynCAMs, and leucine-rich-repeat proteins. Cell-adhesion molecules mediate trans-synaptic signaling, and shape neural network properties by specifying synaptic functions.

Presynaptic boutons are found along axons or at their tips, and are filled with synaptic vesicles (SVs). As action potentials reach presynaptic terminals, the resulting depolarization opens voltage-gated calcium channels within the presynaptic plasma membrane, leading to an influx of calcium. This, in turn, causes docked SVs to fuse with the active zone membrane. As SVs fuse, neurotransmitter is released into the synaptic cleft. Released neurotransmitter then acts on the postsynaptic cell, opening neurotransmitter-gated ion channels and/or activating metabotropic neurotransmitter receptors. The fusion of SVs with the presynaptic plasma membrane is under tight temporal and spatial control: the SVs only dock, fuse, and release neurotransmitter at a restricted and highly specialized area of the presynaptic plasma membrane termed the active zone (AZ). The AZ is tightly associated with an electron-dense proteinaceous cytoskeletal matrix, which is referred to as cytomatrix at the active zone (CAZ). CAZ proteins such as Bassoon (BSN), Piccolo (PCLO), Liprins, ERCs, Velis and Mints are structural components of the presynaptic terminal tethering SVs to the active zone while proteins such as RIM and Munc13 prime them by promoting SNARE complex formation. In addition, the SNARE proteins SNAP-25 and syntaxin that are located within the CAZ interact with VAMP2 on SVs to enable SV fusion with the plasma membrane. After exocytosis, SVs are retrieved by clathrin-dependent endocytosis and are locally recycled to regenerate exocytosis-competent vesicles.

The postsynaptic side of the synapse is specialized to receive the neurotransmitter signal released from the presynaptic terminal and transduce it into electrical and biochemical changes in the postsynaptic cell. The cardinal functional components of the postsynaptic specialization of excitatory and inhibitory synapses are the ionotropic receptors for glutamate and g-aminobutyric acid (GABA), respectively. Most excitatory glutamate receptors NMDA and AMPA receptors are located at dendritic spines, whereas inhibitory glycine receptors and GABA-A receptors are mainly located at dendritic shafts.

These receptor channels are concentrated at the postsynaptic membrane and embedded in a dense protein network comprised of anchoring and scaffolding molecules (DLG4-DLGAP-SHANK complex/ gephyrin, dystrophin-glycoprotein complex), signaling enzymes (Rho-GTPases), and cytoskeletal components (actin filaments, microtubules). Excitatory and inhibitory postsynaptic specializations are quite different in molecular organization, the inhibitory postsynaptic specialization is much less elaborate than the postsynaptic density (PSD) of excitatory synapses.

Signaling Pathway Categories: Neurotransmitters and Other Nervous System Signaling; Organismal Growth and Development

Top Functions & Diseases: Cellular Development; Cellular Growth and Proliferation; Nervous System Development and Function

Molecules: **show preview** Action potential, Adaptor protein 2, ADCY, Adhesion of neuronal cells, ADP, AFDN, Akt, Ampa Receptor, APOE, Apoptosis of neurons, ARHGEF7, Arp2/3, ATP, Axonal Guidance Signaling, BAD, BDNF, Binding of synaptic vesicles, BRAF, Branching of actin filaments, Ca2+, Cadherin, CADM1, Calmodulin, CAMK2, CDC42, CDK5, Cell-cell adhesion of neurons, CFL1, CHN1, cholesterol, CLASP2, Clathrin mediated endocytosis of vesicles, Complexin, Creb, CRK, CRK/CRKL, CRKL, CTNNB1, CTNND1, cyclic AMP, DAB1, Density of synaptic spine, Depolarization of cellular membrane, Development of synaptic spine, diacylglycerol, Differentiation of presynaptic terminals, DLG4, DNAJC5, Docking of synaptic vesicles, Efna, EFNB, EIF4EBP, Endocytosis of protein, EPHA, Ephb, ERK1/2, Exocytosis of synaptic vesicles, FARP1, Formation of mushroom spine, Formation of spot-like adhesion site, Function of neurotransmitter, Fusion of synaptic vesicles, GRB2, GSK3B, HSPA8, inositol triphosphate, Intersectin, ITPR1, KALRN, L-glutamic acid, LIMK1, Loss of dendritic spines, LRP1, LRP8, LRRTM2, MAP1B, MAPK14, MAPT, MARCKS, Maturation of dendritic spines, mGluR, MTOR, Munc18, N-type Calcium Channel, Nap, NECTIN1, NECTIN3, Neurexin, Neuroligin, NMDA Receptor, NSF, NTRK2, NWASP, Organization of synapse, Outgrowth of neurites, p70 S6k, PAFAH1B1, PAK1, PI3K (complex), Pka, PLC gamma, Priming of vesicles, PRKCD, PRKCE, RAB3A, Rab5, RAC1, RAF1, Rap, RAPGEF1, RAS, RASGRF1, RASGRP1, RASGRP2, RELN, RHOA, Scaffolding of postsynaptic region, Sfk, SGTA, Shc, SNAP25, Snare, Sos, Stabilization of microtubules, Stabilization of synapse, Synapsin, Synaptotagmin, SYNGAP1, Syntaxin1, Synuclein, Thrombospondin, TIAM1, TLN1, Translation of protein, UNC13A, VAMP2, VLDLR, WASF1

Drug Summary - Overview of drugs targeting molecules in Canonical Pathway

Showing 3 of 623 row(s) of Drug data.

Drug Name	Targets	Actions	Brand Names	Indications/Status
(2S)-2-{[9-(propan-2-yl)-6-({[4-(pyridin-2-yl)phenyl]methyl}amino)-9H-purin-2-yl]amino}butan-1-ol	CDK5	inhibitor		
(Ala9)-autocamtide-2	CAMK2	inhibitor		
(S)-ketamine	NMDA Receptor	receptor antagonist activity	Spravato	allergic rhinitis/Phase 1 analgesia/Unspecified phase anesthesia/Phase 2

Target Information - Overview of known drug targets in Canonical Pathway

Showing 3 of 92 row(s) of Target data.

Target (Gene Symbol)	Entrez Gene Name	Location	Type	Drug(s)	Species
Akt		Cytoplasm	group	afuresertib, Akt inhibitor XI, AT13148, ipatasertib, MSC2363318A, ONC-201, SR-13668, TAS-117, TAS0612	Human, Mouse, Rat
AKT1	AKT serine/threonine kinase 1	Cytoplasm	kinase	A-443654, AKT inhibitor XIII, archexin, ARQ 751, BAY1125976, capivasertib, CCT129524, enzastaurin, GSK690693, ipatasertib, LY2780301, miransertib, MK2206, MPT0E028, perifosine, triciribine, triciribine phosphate, uprosertib	Human, Mouse, Rat
AKT2	AKT serine/threonine kinase 2	Cytoplasm	kinase	AKT inhibitor XIII, BAY1125976, CCT129524, enzastaurin, GSK690693, triciribine, triciribine phosphate	Human, Mouse, Rat

Supporting References - References from which the Canonical Pathway was derived, received 39 of 39 total references