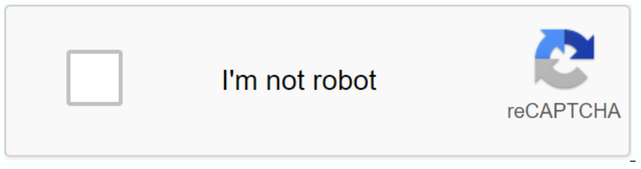


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# Synaptic signaling pathway

Biology Project > Cell Biology > Cell Signaling > Problem Set Cell Signaling Problem Set Problem 4: Types of signals tutorial help answer the question Cell excludes growth factors that have a slow diffusion rate, and interaction only with other cells in the immediate area is an example of _____ signaling. A. Exocrine B. synaptic C. paracrine D. cell contact Autocrine signal signal types bind to receptors on cells that secrete them. Paratron signals bind to receptors and stimulate surrounding cells. Exocrine signals occur when cells secrete signaling molecules into the blood. For example, the ovaries in women and testicles in men are stimulated by hormones produced in the brain. Synaptic signalling is similar to paracritical signalling, but there is a special structure called synapses between the original cell and the cell receiving the signal. Synaptic signaling occurs only between cells with synapses; neuron and muscle that is controlled by neural activity. The signalling contact of the cells must have cells with adjacent plasma membranes. Later, you will learn that cells are altered by their immediate environment and signaling molecules from other cells. Problem 4 | Reply | Problem 5 Biology Project > Cell Biology > Cell Signaling > Problem Set Biology Project Department of Biochemistry and Molecular Biophysics University of Arizona May 2002 Revised: August 2004 Contact Development Team All Copyright Content © 2002-04. All rights reserved. Neurotransmission takes place in synapses, highly specialized points of contact between neurons. Transmission through synapses occurs through a variety of mediators, including amino acid neurotransmitters, peptides, electric current, and even gaseous messengers. The processing of these signals is carried out by receptors, ion channels, and signaling molecules that are grouped in synapses. However, the molecular mechanisms that compile these components in synapses remain largely unknown. Some insight into these mechanisms has been revealed from studies of neuromuscular junction (NMJ), a prototypical chemical synapse where the release of acetylcholine from motor neurons signals muscle contraction. During the development of nicotine acetylcholine receptor muscles (nAChRs), they are grouped on the muscle end plate in response to signals from the presynaptic motor neuron. The 43 kDa protein of the muscular cytoskelete, rapsyn, has been shown to disrupt the gene necessary for grouping nAChRs and may anchor receptors to the subsynaptic cytoskeletic complex (). Similarly, in the central nervous system, the gephyrin protein can mediate synaptic grouping of glycine receptors, which are remotely associated with muscle pain. Gephyrin interacts directly with glycine receptor subunits and treatment with neurons of neurons oligonucleotides of gephyrin interferes with the grouping of glycine receptors (). Despite their similar grouping functions, rapsyn and gephyrin are neither related nor members of larger families of cluster molecules that could provide insight into how other receptors and synaptic components are grouped together. Unlike specialized rapsyn and gephyrin proteins, a large class of proteins containing PDZ domains play a general role in locating channels, signaling enzymes, and adhesion molecules at cell-cell contact sites, including synapses. These functions are illustrated by defining a family of PDZ proteins (PSD-95, Dlg and ZO-1), known as MAGUKs for membrane-associated guanylate kinases. Maguk proteins include PSD-95/SAP-90 and closely related PSD-93/chapsyn-110, SAP-97/hdlg, and SAP-102, all of which are found in synapses in the brain; homologue Drosophila PSD-95/SAP-90, DLG A, which is located at septate junctions and larvae nmj; zo-1 and ZO-2, which are associated with close connections between epithelial cells. Maguks share a common domain organization, with one or three N-terminal PDZ motifs, sh3 domain and C-terminal region homologous guanylate kinase. PDZ domains mediate protein-protein interactions and usually bind to short amino acid motifs to C termini interaction proteins that contain certain ion channels and receptors. Like rapsyn and gephyrin, MAGUKs can directly cluster interaction receptors in synapses. However, there is evidence that MAGUKs play other roles in synaptic organisation by linking interacting receptors with downstream signal transducuues enzymes and regulating the structure and adhesion of synaptic crossings. PSD-95 was initially identified as an ingredient in post-synaptic density and subsequently demonstrated to bind to intracellular C termini glutamate receptors of the NMDA type and shaker K+ channels. These target proteins end with an -E-S/T-D-V* sequence that plagues their interactions with PSD-95 PDZ domains. All three PSD-95 PDZ domains and homologues have similar peptide binding preferences and interact with proteins that break down -E/Q-T/S-X-V/I* (where X means any amino acid), while PDZ domains in other proteins have different binding specifics (). The specificity of c-terminal binding is consistent with the three-dimensional structures of PDZ domains, which were established in the complex with C-terminal peptides (). Functionally, the interaction of PSD-95 with membrane proteins may mediate grouping. When cotransfected with NMDA receptor subunits or Kv1.4 channels, PSD-95 forms large clusters along with interacting channels. These PSD-95/ion channel clusters are not found when proteins are expressed separately or when C-terminal PDZ-binding motifs are mutated (). Although these results indicate the role of PSD-95 in receptor grouping, for in vivo clustering comes from genetic analysis in Caenorhabditis elegans. Here, MAGUK protein LIN-2 and other PDZ protein LIN-7 are both needed to locate the EGF receptor at the cell junction between epithelial cells (). Further genetic evidence was provided by the DLG study, Drosophila psd-95 approver. DLG localizes to glutamatergic synapses in the larvae nmj, where it collakalizes and interacts with group shaker K+ channels. Importantly, grouping Shaker K+ channels requires a PDZ domain DLG(). Shaker channels fail to cluster in dlg null mutants, but clusters typically run in mutants with errors in the SH3 or guanylate kinase (GK) domains. Conversely, the C-terminal removal shaker channel cancels channel clustering even if the DLG remains on the NMJ (). In fact, the C-terminal tail shaker is sufficient to localize proteins into the synapse. Chimera protein containing the whole intracellular C terminus Shaker associated with the extracellular and transmembromenic region of the CD8 clusters on the NMJ in transgenic flies expressing this chimera in the muscles. Similar to grouping Shaker psd-95 in heterologous cells, amino acids on the C terminus channel are needed for synaptic grouping of chimeric protein, such as the presence of DLG (). Evidence of a role for the PSD-95 group of mammals in the grouping of K+ channels and NMDA receptors comes mainly from experiments in cultured cells. As mentioned above, PSD-95 can cluster these proteins when coexpressed in heterologous cells. Also, mammalian MAGUKs can replace DLG to mediate grouping in Drosophila, indicative of preserved function (). However, a recent study on nmda receptor grouping in synapses in neuronal cultures showed that NMDA receptors initially form non-synaptic clusters that do not have PSD-95 (). This suggests that NMDA receptors may initially aggregate in the absence of PSD-95, and their association with PSD-95 may work to maintain preformed receptor clusters in synapses. It is also possible that other PSD-95 family members cluster NMDA receptors before they are targeted at synapses. Genetic disruption of PSD-95 and its relatives will be necessary to resolve these issues. In addition to PDZ themes, MAGUKs contain several preserved domains indicative of a role in signal transmission. Maguks all have SH3 domains, a protein-protein interaction motif found in various signaling proteins. However, no binding partners have yet been identified for the MAGUK SH3 domain. The presence of a GK domain that catalyzes the conversion of GMP into GDP by ATP indicates a signal; however, critical amino acids needed to bind ATP are not stored in many MAGUK and no cochase activity has been detected. A family of proteins that interact with the GK domain PSD-95 has been identified called SAPAPs or GKAP (). These proteins are not homologous to known proteins and their function remains unknown, although they have the potential to play a role in the multimerisation of PSD-95 (see below). A subset of MAGUKov, which contains LIN-2 and its homological CASK mammals, also contains the domain CaMKII, but again this domain lacks amino acids critical to the activity of the cinema. Further evidence that MAGUKs organise signalling cascades results from their interactions with signalling proteins such as neuronal oxide (nNOS; ). This occurs through PDZ-PDZ interaction, in which the second domain PDZ PSD-95 binds one PDZ domain in the nNOS. In many central neurons, nNOS activity is selectively stimulated by Ca2+ through NMDA receptors, while Ca2+ input through other channels is not as effective. The binding of PSD-95 to both NMDA and nNOS receptors may provide scaffolding to selectively link nNOS to the Source of NMDA receptor Ca2+. Both NMDA receptor subunits and nNOS may interact with the same PSD-95 molecule to form an in vitro theern complex. In addition, internalisation of a peptide that disrupts PDZ interactions into brain granular cells prevents nmda receptor-mediated nNOS stimulation, but does not affect the flow of Ca2+ through NMDA receptors. Many neuronal populations lack nNOS and in these cells PSD-95 can link different signaling molecules to NMDA receptors. Indeed, the recently identified ras-GTPase protein activation, p135 SynGAP (3Chen H.-J Rojas-Soto M Oguni Kennedy M.B.), interacts with all three domains of PDZ PSD-95 and colocalizes on synapses with NMDA receptors and PSD-95. A critical source of regulation is the proposed phosphorylation of SynGAP CaMKII, and inhibition of rasGAP activity in isolated postsynaptic densities by active CaMKII (Chen et al. 1998Chen H.-J Rojas-Soto M Oguni Kennedy M.B). CaMKII is a rich PSD protein that is activated by Ca2+ through NMDA receptors. Analogous to the nNOS, the interaction of SynGAP with PSD-95 may link its regulation to the NMDA receptor gate of the Ca2+ pathway. Such a model would help explain how Ca2+ tide through NMDA receptors activates MAP kinase cascades in neurons. NMDA receptors are also needed to induce certain forms of synaptic plasticity, such as long-term potentiation (LTP) in the CA1 area of the hippocampus, and C-terminal binding proteins of NMDA receptor subupons may play a central role in this process. To evaluate the functional role of nmda receptor cytoplasmic domains, the c-terminal tails of NMDA R2A, -B or -C subumers units were removed by genetic targeting in mice, thus these proteins could not interact with PSD-95 or associated proteins (). The phenotypes of these mice closely resemble the types of corresponding gene knockouts, indicating that C termini are critically involved in NMDA receptor function. Mouse tail C-terminal NR2A had deficits in LTP in CA1 and in spatial education. Although receptor localization was not closely investigated, synaptic NMDA currents were normal in these mice. Therefore, there is a deficiency in LTP after activation of the NMDA receptor, suggesting that interactions of the NR2A tail with PSD-95, GAPSYN, or other proteins are necessary for LTP. In addition to organising signalling complexes, MAGUKs can affect synaptic structure through interactions with adhesion molecules. Indeed, mutations in DLG change synaptic structures to Drosophila NMJ. On the postsynaptic side, the NMJ larva is surrounded by a subsynaptic reticullum, a system of convoluted membranes of homologous to connecting folds of NMJ vertebrates. In dlg mutants this structure is normal in the early larvae stages, but fails to properly expand and develop as the muscle grows. On the presynaptic side, mutations in DLG increase the number of active zones per bouton. One clue to how DLG affects synaptic structures is that DLG clusters fasciclin II (Fas II), an NCAM-like adhesion molecule, on the Drosophila NMJ in a similar way shaker the K+ channel (, ). II works in synaptic stabilization and growth, and without it synapses retract after larvae development. Manipulation of the level of expression II changes the degree of synaptic growth and down-regulation of LEVELS II activity leads to an increase in synaptic growth. Therefore, one attractive model is that the activity antagonizes the interaction between DLG and II, thereby reducing the level of protein II grouped in the synapse and allowing structural plasticity. The preserved function for mammalian magukes in regulating the synaptic structure is designed by the ability of PSD-95 homologues to save the phenotype of dlg mutants, including grouping II, in nmj. In addition, two members of the MAGUK mammalian family interact with different cell adhesion molecules: PSD-95 binds the C-terminal tail of neurolilines (NL) and CASK binds the tail of neurexins (). While the functions of these surface molecules are not fully understood, a subset of β-neurexins interacts with neurolilines and can form heterotypic intercellular connections when expressed on different cells. PsD-95 and CASK can therefore regulate cell adhesion and structure through these interactions. The mechanism by which PSD-95 and its homologues falsify molecular grouping is uncertain. Data from Drosophila using the CD8/Shaker K+ channel chimeric protein (described above) suggest that the Shaker channel is initially focused evenly on the membrane and is then actively grouped or selectively stored in the DLG synapse. One clustering model suggests that the first and second PDZ domains psd-95 each bind the tail of the NMDA receptor or shaker channel subunits while each channel because it exists as binds multiple psd-95 molecules, leading to aggregation of these two proteins. Also, GKAPs can bind to GK domains of multiple PSD-95 molecules, similarly contributing to aggregation. However, this model cannot explain how N terminus and one PDZ domain PSD-95 are sufficient to cluster Shaker K+ channels or NMDA receptors in heterologous cells (). Alternatively, PSD-95 can itself oligomerize and thus aggregate protein interaction. To support this model, two preserved N-terminal cysteine residues in PSD-95 were found necessary for protein multimerization and K+ channel grouping in transfected cells (). Under non-reducing conditions, these cysteins can form disulfide bonds, allowing multimerization of PSD-95 molecules. However, these cysteines are also sites of palmitoylation (). Palmitate is an fatty acid that is enzymatically added to specific proteins in a reversible manner and that dynamically regulates protein interactions with lipid bilayers. PSD-95 in the brain and in transfected COS cells is palmitoylized, and mutations in one of the N-terminal cysteins disrupt palmitoylation and the connection of PSD-95 with the membrane and Kv1.4. Therefore, N-terminal cysteines are important in locating PSD-95 to the membrane so that they can be associated with transmembrome proteins (Figure 1). Questions therefore remain as to whether PSD-95 can multimerize in a cell reducing environment, and whether multimerization is necessary for receptor grouping. Figure 1Postsynaptic interactions of PSD-95View the full caption (A) N-terminal palmitoylation (jagged lines) targets PSD-95 on synaptic membranes and promotes the association of PSD-95 with membrane proteins, including the NMDA receptor. (B) PSD-95 then aggregates and organises synaptic proteins either through active grouping or selective retention of interaction proteins. Through these mechanisms PSD-95 can both assemble a signal of the transduction pathway and help determine the synaptic structure. Maguk-receptor cluster stabilisation appears to be mediated by interactions with cytoskeleton. In erythrocytes, the MAGUK p55 protein binds protein 4. A similar interaction between neural MAGUKs and protein 4.1 family members in synapses could help link NMDA receptors and K+ channel clusters to actin-rich cytoskeleton. The NMDA R1 subunit also interacts with actin-binding α, which provides an additional cytoskeletal contact point. The newly identified PSD-95 binding protein, CRIPT, may also mediate the link between PSD-95 and tubulin-based cytoskeleton (). CRIPT collates with PSD-95 in synapses and coimunoprecipitates with PSD-95 and tubulin from the brain. When PSD-95 and CRIPT are co-expressed in heterology PSD-95 is transferred from diffusion localization to colocalization with CRIPT in the cytoskeletone of the microtubule. CRIPT therefore provides a possible link between PSD-95 and another intracellular structure. While our understanding of synaptic organization has been helped by the discovery of maguks, much work remains. The most critical evidence for MAGUKs in clustering receptors, organizing signaling cascades, and influencing synaptic structure comes from studies of Drosophila NMJ, and it is unclear how this is related to synapses in the nervous system of mammals. It is also not known how MAGUKs are themselves aimed at synapses, and questions remain about how to recruit interacting proteins there. The study of PSD-95 and relatives promises to improve our understanding of synaptic structure, function and plasticity. DOI: 00)81179-4