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Chapter 1 : Membrane Channels and Pumps - Biochemistry - NCBI Bookshelf

The expression and physiological properties of receptors, ion channels and transporters shape the electrical and biochemical properties of individual neurons and neural circuits. These membrane proteins are targets for drugs for the treatment of neurological conditions and also interact with.

Membrane Transport Mechanisms Diffusion The hydrophobic layer of the plasma membrane creates a barrier that prevents the diffusion of most substances. Exceptions are small molecules such as gases like nitric oxide NO and carbon dioxide CO2 , and nonpolar substances such as steroid hormones and fatty acids. Even though fatty acids can diffuse across the plasma membrane, this occurs slowly. Recent work indicates that a substantial amount of fatty acid transport is via carrier proteins. Transport of polar substances depends upon transmembrane proteins. Channels Channels are large proteins in which multiple subunits are arranged in a cluster so as to form a pore that passes through the membrane. Each subunit consists of multiple transmembrane domains. Most of the channels that we will consider are ion channels. Another important type of channel protein is an aquaporin. Aquaporins are channels that allow water to move rapidly across cell membranes. Movement through a channel does not involve specific binding see facilitated diffusion below. The two factors that affect the flow of ions through an open ion channel are the membrane potential and the concentration gradient. Note that when ions move through a channel across a membrane, this changes the membrane potential depolarization or hyperpolarization. Changes in membrane potential are used to code information, particularly in the nervous system. See the web page on Membrane Potentials. Properties of Ion Channels For any ion channel, there are two important properties to consider: Most ion channels are specific for one particular ion. Gating refers to what opens or closes a channel. Below we classify different ion channels according to the type of gating. Ungated A few types of ion channels are ungated, meaning they are open all the time. Voltage-gated Voltage-gated ion channels open or close in response to changes in membrane potential. Voltage-gated ion channels are key in the generation of electrical signals in nerve, muscle, and cardiac cells. Ligand-gated Ligand-gated ion channels are opened when regulatory molecules bind to the channel protein. Many neurotransmitter receptors are ligand gated ion channels. An example is the nicotinic acetylcholine receptor. This is the receptor that is found at the neuromuscular junction on skeletal muscle cells, and also at synapses in autonomic ganglia. Mechanically-gated Afferent neurons sensory neurons in the skin that respond to touch or stretch have ion channels in their sensory dendrites that open in response to pressure or other mechanical changes at the cell membrane. Mechanically-gated channels are also found in the specialized sensory cells of the auditory and vestibular system. Temperature-gated There are also afferent neurons that sense warm and cold and possess temperature-gated ion channels in their sensory dendrites. While these ion channel proteins are normally gated by temperature, it turns out that certain ligands also can open them. For instance, capsaicin, the molecule found in chili peppers, opens the channel that is normally opened by noxious heat, while menthol opens the channel that is normally opened by cool temperatures. Facilitated Diffusion Facilitated diffusion is transport involving a carrier protein that has a specific binding site for the transported substance. An example is the movement of glucose from the extracellular fluid into cells glucose uptake. The transport protein, known as the glucose transporter, has a specific binding site for glucose. The binding of glucose changes the conformation of the glucose transporter, which can exist in different conformations that expose the binding site to either the extracellular fluid or the cytosol. The concentration gradient for glucose determines the rate and direction of transport. Facilitated diffusion is a passive process, meaning that it does not require ATP. With glucose uptake, glucose is transported from the extracellular fluid into the cytosol, where cells metabolize it as a source of energy. However, if the glucose concentration is higher inside the cell than outside, the direction of transport will be in the opposite direction. Facilitated diffusion and other processes that depend on membrane transport proteins are regulated by controlling the number of transport proteins present in the membrane. For instance, glucose uptake is

regulated by the hormone insulin. At low concentrations of insulin, few glucose transporters are on the plasma membrane. Insulin stimulates glucose uptake by causing vesicles containing glucose transporters to fuse with the plasma membrane, as shown in the figure. Coupled Transport Coupled transport is similar to facilitated diffusion in that it involves specific binding, however in this case, two substances are required to bind in order for transport to occur. As a consequence, the free energy driving the transport is the sum of the free energies for transport of both substances. If the transported substances move in the same direction across the membrane, it is called cotransport; if they move in the opposite direction, it is called countertransport. The transport of glucose across the apical plasma membrane of epithelial cells in the small intestine is an example of cotransport. This is the first step in the absorption of glucose from the foods you eat. The transport protein is known as the sodium-glucose cotransporter. Immediately after eating a lot of carbohydrates, the concentration gradient of glucose will favor transport into cells, but as more and more glucose is absorbed, that will not be the case. Because they both involve specific binding, facilitated diffusion and coupled transport show saturation. Transport depends upon a limited number of transport proteins in the membrane, each of which must bind with the transported substance for a given period of time. As the concentration of the transported substance increases, the rate of transport also increases, but then starts to level off and approach a maximum. At high concentrations, there comes a point where every transporter in the membrane is bound by the transported substance, and the transport rate cannot increase beyond this transport maximum Vmax. Active Transport Active transport describes the process whereby the transport of specific substances is coupled to ATP hydrolysis. Because the energy for transport is derived from ATP hydrolysis, these transporters effectively move substances in one direction, regardless of the concentration gradient. These ionic gradients underlie electrical excitability in neurons and muscles. ABC proteins have a particular molecular structure that includes two nucleotide binding domains where ATP binds. An example is the multidrug resistance protein MDR1 also known as P-glycoprotein. This protein uses the energy of ATP hydrolysis to pump a wide variety of nonpolar drugs and toxins out of cells. It is called "multidrug resistance" protein because over-expression of MDR1 in tumor cells confers resistance to chemotherapy drugs. CFTR forms a Cl- channel that is expressed on the apical plasma membrane of many epithelial cells. CFTR is the protein that is defective in the genetic disorder cystic fibrosis. CFTR plays a key role in the secretion of ions and water across epithelia see page on Epithelial Transport. Some bacterial toxins cause unregulated activity of CFTR, resulting in excessive secretion in the small intestine which causes diarrhea. In cystic fibrosis, CFTR channels are defective or absent, leading to decreased secretion, which causes pathology in the lungs and digestive system.

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Chapter 2 : Neurotransmitter Receptors, Transporters, and Ion Channels Research Areas: R&D Systems

The acetylcholine receptor is a ligand-gated channel in that the channel opens in response to the binding of acetylcholine (Figure). In contrast, the sodium and potassium channels, which mediate action potentials in neuron axon membranes, are opened by membrane depolarization rather than by the binding of an allosteric effector.

Membrane Transport Mechanisms Substances Not Requiring a Membrane Protein Nonpolar substances often can diffuse straight through the lipid bilayer without requiring a membrane protein. Examples include oxygen, fatty acids, steroid hormones, and general anesthetics. Although keep an open mind about possible exceptions here. Certain small polar molecules can diffuse through the lipid bilayer. Carbon dioxide and, to a limited extend, water fall in this category. Ungated Ion channels provide actual holes through which the ions can diffuse across the membrane. No binding takes place. A few are open all the time and thus are ungated. Much cellular regulation revolves around this point. Voltage-Gated Ion channels that open or close in response to changes in the membrane potential are termed voltage-gated. Ligand-Gated Many ion channels are ligand-gated; that is, they open in response to the binding of an extracellular or intracellular regulatory molecule. An important example is the the acetylcholine receptor found in the membrane of skeletal muscle cells. These open in response to neurotransmitter acetylcholine released by the neurons that cause muscle contraction. This ion channel has five subunits, which is a characteristic of an important class of neurotransmitter receptors in the brain. Recall that the acetylcholine receptor is the protein attacked by antibodies in myesthenia gravis. This ion channel plays a role in the secretion of insulin from the pancreas. More on this later in the quarter. Mechanically Gated Examples of ion channels that open in response to mechanical movement of adjacent structures include touch sensors in the skin and vibration sensors in the inner ear that respond to sound. Also, most hollow organs, such as the bladder, intestines and heart, have stretch sensors that respond to expansion of the organ. Temperature-Gated Some ion channels are temperature-gated. These are found in sensory neurons in the skin and mucous membranes and open with either an increase in temperature or decrease in temperature. This, of course, leads to the sensations of warm and cold. Some temperature gated ion channels are interesting because some plants contain molecules that open the ion channels, despite the fact that they are normally temperature-gated rather than ligand-gated channels. The most important is an ion channel that normally opens in response to noxious heat, but that also responds to capsiacin, the substance that gives chili peppers their special characteristic. Which national cuisine makes the best use of these ion channels? Can you think of a chemical substance that opens ion channels that normally respond to cooooool stimuli? Answer Facilitated Diffusion Facilitated diffusion is based on transporters that must specifically bind the substance to be transported. The binding causes a conformation change, which allows the transported substance to be released on the other side of the membrane. In facilitated diffusion, the energy is provided by the concentration gradient of the substance transported. If the concentration of the substance is higher outside the cell than inside, the substance moves inward. Conversely, if the concentration is higher on the inside than on the outside, the substance moves outward. No ATP is required. Due to the specific binding step, a facilitated transporter can saturate if the concentration of the transported substance becomes high enough. Once this happens, no further increase in the rate of transport can occur, since the binding site on the transporter is occupied essentially all the time. By contrast, this does not occur with ion channels. As the concentration of the ion increases, the amount that moves through the pore of the channel increases proportionately. There is no process that becomes saturated. The glucose transporter is a widespread and important example of this type of transporter, especially since insulin controls the number of these transporters working in certain cells. When more insulin is present, more of these transporters are added to the membrane of cells such as those in muscle. As a result, more glucose moves into the muscle cells. The figures shows how this takes place. Insulin leads to exocytosis of vesicles containing glucose transporters. Then, when the insulin concentration in the blood decreases, endocytosis removes some of the glucose

transporters and thus less glucose moves into the muscle cells. In this same way, the number of various transporters or ion channels can change depending on the specific circumstances. Cotransporters Cotransporters are similar to those in facilitated diffusion in that specific binding takes place and no ATP is expended. It is different in that two substances must bind at the same time before the transport takes place. The requirement that two substances must be transported together creates a major additional consideration in the energetics. The free energy driving the transport is the sum of the free energys for both substances. Suppose someone eats a donut. Countertransporters work on similar principles, except the two transported substances move in opposite directions across the membrane. Active Transport Active transport is similar to the preceding two mechanism in that specific binding of the transported substance occurs. However, here ATP is required in a step in which the transporter is phosphorylated. Because energy is provided in this way, the transporter can move the substance to a higher concentration. Thus, these transporters always move the transported substance in one direction, regardless of the concentration gradient. The later, for example, are found in the stomach and participate in the secretion of acid into stomach. One example is the CFTR Cl- ion channel found in epithelia lining the intestines and in the airways in the lungs. It opens when it is phosphosphorylated. In the small intestines, this ion channel opens in response to certain bacterial toxins causing diarrhea. Also, this ion channel is defective in cystic fibrosis, a genetic disorder. Another example, is the multi-drug resistance transporter MDR transporter. Using ATP energy, it transports various nonpolar molecules out of the cytosol of cells. The cells in liver tumors often express much larger quantities of the MDR transporter than normal. This can make chemotherapy against the tumor cells more difficult than might be expected, since the MDR transporter actively removes the chemotherapy agent from the cell.

Chapter 3 : Summary of Membrane Transport

Membrane Receptors, Channels and Transporters in Pulmonary Circulation is a proceeding of the Grover Conference (Lost Valley Ranch and Conference Center, Sedalia, Colorado; September ,), which provided a forum for experts in the fields of those receptors, channels and transporters that have been identified as playing key roles in.

This process is called transduction: Hundreds of receptors are known and there are undoubtedly many more yet to be discovered. Many drugs exert their therapeutic effects by activating or blocking membrane receptors. Membrane receptors were postulated to exist long before there was any direct evidence for them. The first evidence came from work by the English physiologist Langley on nerve synapses , as long ago as He painted a solution of the drug nicotine on to ganglia nodules on sympathetic nerves, containing synaptic connections between axons from the central nervous system and nerve cells whose postganglionic fibres run out to innervate organs such as the heart, eye, and gut. Langley noted that the nicotine caused excitation, then inhibition, of the organs innervated by the postganglionic nerves, implying that it had activated and then blocked the nerveâ€"nerve junctions in the ganglion. Similarly, when nicotine was put on to the junction between motor nerve endings and skeletal muscle fibres, the muscle fibres twitched, suggesting that it mimicked chemical signals released by motor nerves. The demonstration of chemical transmission had to await the Nobel prize-winning discovery of the German pharmacologist Otto Loewi, reported in Following an idea for an experiment that he had in a dream, Otto Loewi set up 2 perfused frog hearts such that the perfusate from the first flowed over the second. When the vagus nerve attached to the first heart was stimulated that rate of beating slowed; after a few seconds so did that of the second heart. Thus the idea was born that there exist receptive sites to receive chemical signals although this experiment did not prove that the effector substance came from the vagus nerve itself. Identification of binding sites Not until the s were attempts made to look for specific binding molecules in cell membranes. Waser used radioactively-labelled curare â€" which is known to block the receptors for acetylcholine , the neurotransmitter released by motor nerves in skeletal muscle â€" and showed, by autoradiography photographic detection of radioactivity , that the material was bound to the muscle at the neuromuscular junction , exactly where the nerve fibres contacted the muscle. In another seminal study, the British pharmacologists William Paton and Humphrey Rang used radioactive atropine to bind to smooth muscle membranes, where atropine was known to prevent the action of acetylcholine at parasympathetic nerve endings. They detected specific binding molecules of finite size and were thus able to quantify, for the first time, the number of acetylcholine receptors known here as the muscarinic type present in smooth muscle. Some are hormones , secreted by endocrine glands, and circulating in the blood, which leave through capillary walls to gain access to tissue fluids around their target cells. In general, each receptor is the product of one gene. By now, many receptor genes have been cloned and much is known about the molecular structure and mechanism of the receptors. Agonists and antagonists Any substance that binds to a receptor is known as a ligand: However, many drugs cause their therapeutic actions on the body by specifically binding to particular receptors. There are two reasons for not using endogenous substances as therapeutic drugs. Firstly, many agonist drugs are actually much more effective at activating their receptor than the naturally-occurring endogenous ligand. Secondly, in the case of drugs that work by preventing overactivity of bodily systems, what is needed is an antagonist that binds to the receptor, blocking the action of the endogenous ligand. You may wonder if all drugs that work by stimulating receptors have equivalent endogenous ligands â€" in other words, whether the drugs are all reinventions of our own internal chemistry. Consider the pain-relieving drug morphine; it is of plant origin and has a formula unlike anything found in the body. Hans Kosterlitz, working in Aberdeen in the s, maintained that for each non-endogenous agonist there is indeed a corresponding endogenous ligand. The same argument now appears to be true for the cannabinoids, found in marijuana, and the benzodiazepines such as Valium , which relieve anxiety. There are still many drugs that are thought to act on naturally-occurring receptors for which there are no known endogenous ligands: The transduction process

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There are important generalizations to be made about receptors and how they transduce their effects. The first consideration is specificity. The body needs to be able to turn on and off specific processes as they are needed. If you are frightened and fleeing from an attacker you do not need to salivate or digest your last meal, but you do need to mobilize all the mental and physical energy you can. Yet there are only a few ways in which a cell can switch on or off a process. For example there are two types of histamine receptor, H1 and H2. H2 receptors are confined to a few sites, including the stomach, where they are involved in acid production, explaining why the antihistamines that block only the H1 receptor used to treat allergies do not prevent gastric acid formation. Different types of cells are programmed by their genes to make only some receptor types and to locate them appropriately. In this way the body is able to respond in a very specific way to different situations. How do receptors transduce? Clearly, if a receptor is to receive an external chemical signal, part of the protein molecule must be outside the cell. This is the recognition site, which binds specifically with the messenger molecule. When antagonists are bound, the recognition site is blocked and nothing further need happen. Normally antagonists have a high affinity, so that they bind tightly to the receptor for a long period of time. When endogenous or exogenous agonists bind to the receptor then something further must happen in order to transduce the effect. While agonists have a high specificity for the binding sites, their affinity is low, so they are soon released to allow further activation by another agonist molecule. For example, when you walk, many groups of muscle fibres in the legs, arms, and torso undergo rapid contractions and relaxations: However, when an anaesthetist wants to relax your abdominal muscles for surgery, a long-acting blocker an antagonist is used. The recognition site in each receptor is joined to the rest of the protein molecule by the transmembrane domain â€” a chain of amino acids that crosses back and forth across the membrane, ending up with an intracellular terminus. The number of membrane crossings is variable, between as few as two and as many as twelve. Types of receptor There are three main receptor families: Here, the intracellular domain of the receptor is bound to one of many sorts of G-protein G-proteins are so-called because of their high affinity for guanine nucleotides. For instance, nicotinic receptors in muscle form channels that allow sodium ions to enter the muscle when activated by the neurotransmitter acetylcholine, released by motor nerves or by nicotine. In this state they can stimulate tyrosine kinase enzymes in the cell, leading to further effects. The hormone insulin acts on cells in this way.

Chapter 4 : Membrane transport protein - Wikipedia

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Received Dec 8; Accepted Mar 1. Copyright Panneels et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are properly credited. This article has been cited by other articles in PMC. Abstract Background Membrane proteins MPs play key roles in signal transduction. However, understanding their function at a molecular level is mostly hampered by the lack of protein in suitable amount and quality. Despite impressive developments in the expression of prokaryotic MPs, eukaryotic MP production has lagged behind and there is a need for new expression strategies. In a pilot study, we produced a Drosophila glutamate receptor specifically in the eyes of transgenic flies, exploiting the naturally abundant membrane stacks in the photoreceptor cells PRCs. Now we address the question whether the PRCs also process different classes of medically relevant target MPs which were so far notoriously difficult to handle with conventional expression strategies. Principal Findings We describe the homologous and heterologous expression of 10 different targets from the three major MP classes - G protein-coupled receptors GPCRs , transporters and channels in Drosophila eyes. PRCs offered an extraordinary capacity to produce, fold and accommodate massive amounts of MPs. The expression of some MPs reached similar levels as the endogenous rhodopsin, indicating that the PRC membranes were almost unsaturable. Expression of endogenous rhodopsin was not affected by the target MPs and both could coexist in the membrane stacks. The metabotropic glutamate receptor and human serotonin transporter - both involved in synaptic transmission - showed native pharmacological characteristics and could be purified to homogeneity as a prerequisite for further studies. Significance We demonstrate expression in Drosophila PRCs as an efficient and inexpensive tool for the large scale production of functional eukaryotic MPs. The fly eye system offers a number of advantages over conventional expression systems and paves the way for in-depth analyses of eukaryotic MPs that have so far not been accessible to biochemical and biophysical studies. However, drug discovery as well as detailed biochemical and structural studies are still hindered by a number of problems already encountered in the production of eukaryotic MPs. It is therefore not surprising that the majority of eukaryotic MPs found in the structural database Membrane Proteins of Known 3D-Structure, http: Most of them are localized in specialized cells from i. These cells are adapted to the massive production of MPs, which are often densely packed in their respective membrane environment. In contrast to eukaryotic MPs, our understanding of prokaryotic MPs has tremendously increased in the past decade due to the optimization of bacterial strains and expression tools for MP production [4] , as well as by the use of extremophilic organisms e. Archaea as a source for MPs of increased stability [5]. Bacteria enriched in membranes are widely used for MP expression as they seem to offer increased membrane surface as well as an optimized insertion machinery [6]. The crystal structures of close prokaryotic homologs provided relevant models for many mammalian MPs. However, some eukaryotic MPs which are of prime interest in neuropharmacology, like the sodium-dependent serotonin transporter SERT or 5HTT , do not have close bacterial homologs [7]. Importantly, differences in the active sites have been observed e. The precise architecture of these binding sites can be difficult to model which leads to controversies in the perception of their reaction mechanisms. For MPs regulated by allosteric mechanisms [10] , focusing on the ligand binding site is not sufficient. Among G protein-coupled receptors GPCRs , metabotropic glutamate receptors mGluRs are prototypes for allosteric regulation and have been subjected to random high-troughput ligand screens for drug design as well as structure-based virtual screening [11] , [12]. Both, high-throughput pharmacological and structural analyses of MPs require amounts of material which are often not provided in sufficient quality and quantity by conventional expression systems. Eukaryotic

cells in culture, like insect cells and yeast are commonly used for the overexpression of eukaryotic MPs [3]. However, a major drawback is the often limited capacity of these cells for trafficking, folding and membrane insertion of the target MPs and therefore, a significant portion of immature MPs remain trapped in internal membranes [13]. In a pilot study, we engineered a transgenic fly overexpressing a recombinant Drosophila metabotropic glutamate receptor DmGluRA specifically in the eyes [14]. The idea was to target the receptor to the naturally abundant membrane stacks in the photoreceptor cells PRCs , the rhabdomeres, housing the GPCR-prototype rhodopsin. Drosophila melanogaster was chosen because fly genetics offers the possibility of regulating ectopic expression in intensity, kinetics and localization using specific promoters drivers. The DmGluRA production in fly eyes gave higher yields than the baculovirus overexpression system in Sf9 cells and the receptor was functional. In addition, the purified protein was clearly superior in homogeneity compared to protein obtained from Sf9 membranes [14] which typically suffers from the presence of immature receptors [3]. The receptor could be purified in mg amounts [14] and biochemical analysis suggested cholesterol as an allosteric regulator that switches the receptor to a high affinity state [15]. Recently, the expression protocol was improved by the use of GFP-fusion constructs [16]. However, the question remained whether overexpression in fly eyes would be also applicable to the heterologous expression for MPs like transporters and channels which are often difficult to express in conventional systems. In this study, we show the exceptional properties of the PRCs in offering seemingly unsaturable membrane space for target MP insertion. We establish overexpression in fly eyes as a general, efficient and inexpensive method for large scale production of functional eukaryotic MPs and exemplify our findings with an in depth analysis of mGluR5 and SERT. Results Photoreceptor cells have a large capacity for recombinant MPs The successful expression of a functional Drosophila metabotropic glutamate receptor DmGluRA in fly eyes recommended this system for the production of eukaryotic MPs [14] see Supporting Information: Primer of the fly eye system Primer S1. We now addressed the question whether overexpression in the eyes is superior to overexpression e. The expression driven by eye-specific promoters was impressive compared to the insignificant levels obtained with ubiquitous promoters Figure 1A. Using an eye-specific driver was a prerequisite for high expression.

Chapter 5 : GABAA Receptor Physiology and Pharmacology - Oxford Handbooks

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Extracellular domains[edit] The extracellular domain just externally from the cell or organelle. If the polypeptide chain crosses the bilayer several times, the external domain comprises loops entwined through the membrane. For example, a neurotransmitter , hormone , or atomic ions may each bind to the extracellular domain as a ligand coupled to receptor. Klotho is an enzyme which effects a receptor to recognize the ligand FGF Transmembrane domains[edit] Two most abundant classes of transmembrane receptors are GPCR and single-pass transmembrane proteins. Upon activation of an extracellular domain by binding of the appropriate ligand, the pore becomes accessible to ions, which then diffuse. In other receptors, the transmembrane domains undergo a conformational change upon binding, which effects intracellular conditions. In some receptors, such as members of the 7TM superfamily , the transmembrane domain includes a ligand binding pocket. Intracellular domains[edit] The intracellular or cytoplasmic domain of the receptor interacts with the interior of the cell or organelle, relaying the signal. There are two fundamental paths for this interaction: The intracellular domain communicates via protein-protein interactions against effector proteins, which in turn pass a signal to the destination. With enzyme-linked receptors , the intracellular domain has enzymatic activity. Often, this is tyrosine kinase activity. The enzymatic activity can also be due to an enzyme associated with the intracellular domain. Signal transduction[edit] External reactions and internal reactions for signal transduction click to enlarge Signal transduction processes through membrane receptors involve the external reactions, in which the ligand binds to a membrane receptor, and the internal reactions, in which intracellular response is triggered. Binding of the signal molecule to the receptor protein will activate intracellular signaling proteins that initiate a signaling cascade. The ion channel linked receptor ; The enzyme-linked receptor ; and The G protein-coupled receptor. Ion channel linked receptors have ion channels for anions and cations, and constitute a large family of multipass transmembrane proteins. They participate in rapid signaling events usually found in electrically active cells such as neurons. They are also called ligand-gated ion channels. Opening and closing of ion channels is controlled by neurotransmitters. Enzyme-linked receptors are either enzymes themselves, or directly activate associated enzymes. These are typically single-pass transmembrane receptors, with the enzymatic component of the receptor kept intracellular. The majority of enzyme-linked receptors are, or associate with, protein kinases. G protein-coupled receptors are integral membrane proteins that possess seven transmembrane helices. These receptors activate a G protein upon agonist binding, and the G-protein mediates receptor effects on intracellular signaling pathways. Ion channel-linked receptor[edit] Main article: Ligand-gated ion channel During the signal transduction event in a neuron, the neurotransmitter binds to the receptor and alters the conformation of the protein. This opens the ion channel, allowing extracellular ions into the cell. Ion permeability of the plasma membrane is altered, and this transforms the extracellular chemical signal into an intracellular electric signal which alters the cell excitability. The protein consists of 4 subunits: This receptor can exist in three conformations. The closed and unoccupied state is the native protein conformation. However, this open and occupied state only lasts for a minor duration and then the gate is closed, becoming the closed and occupied state. The two molecules of acetylcholine will soon dissociate from the receptor, returning it to the native closed and unoccupied state. Enzyme-linked receptor Sketch of an enzyme-linked receptor structure structure of IGF-1R click to enlarge As of , there are 6 known types of enzyme-linked receptors: Receptor tyrosine kinases have the largest population and widest application. Most of these receptors will dimerize after binding with their ligands, in order to activate further signal transductions. For example, after the epidermal growth factor EGF receptor binds with its ligand EGF, the two receptors dimerize and then undergo phosphorylation of the tyrosine residues in the enzyme portion of

each receptor molecule. This will activate the tyrosine kinase and catalyze further intracellular reactions. G protein-coupled receptors[edit] Main article: G protein-coupled receptor G protein-coupled receptors comprise a large protein family of transmembrane receptors. They are found only in eukaryotes. These vary in size from small molecules to peptides and large proteins. G protein-coupled receptors are involved in many diseases, and thus are the targets of many modern medicinal drugs. Membrane receptor-related disease[edit] If the membrane receptors are denatured or deficient, the signal transduction can be hindered and cause diseases. Some diseases are caused by disorders of membrane receptor function. This is due to deficiency or degradation of the receptor via changes in the genes that encode and regulate the receptor protein. The membrane receptor TM4SF5 influences the migration of hepatic cells and hepatoma. In the case of poliovirus , it is known in vitro that interactions with receptors cause conformational rearrangements which release a virion protein called VP4. It is proposed that the conformational changes induced by receptor binding result in the attachment of myristic acid on VP4 and the formation of a channel for RNA. Structure-based drug design[edit] Main article: Drug design Through methods such as X-ray crystallography and NMR spectroscopy , the information about 3D structures of target molecules has increased dramatically, and so has structural information about the ligands. This drives rapid development of structure-based drug design. Some of these new drugs target membrane receptors. Current approaches to structure-based drug design can be divided into two categories. The first category is about determining ligands for a given receptor. This is usually accomplished through database queries, biophysical simulations, and the construction of chemical libraries. In each case, a large number of potential ligand molecules are screened to find those fitting the binding pocket of the receptor. This approach is usually referred to as ligand-based drug design. The key advantage of searching a database is that it saves time and power to obtain new effective compounds. Another approach of structure-based drug design is about combinatorially mapping ligands, which is referred to as receptor-based drug design. In this case, ligand molecules are engineered within the constraints of a binding pocket by assembling small pieces in a stepwise manner. These pieces can be either atoms or molecules. The key advantage of such a method is that novel structures can be discovered.

Chapter 6 : Nicotinic Acetylcholine Receptors - Oxford Handbooks

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Either its inner gate is open, or outer gate is open. In contrast, a channel can be open to both environments at the same time, allowing the molecules to diffuse without interruption. Carriers have binding sites, but pores and channels do not. Research has correlated defects in specific carrier proteins with specific diseases. Active transport The action of the sodium-potassium pump is an example of primary active transport. The two carrier proteins on the left are using ATP to move sodium out of the cell against the concentration gradient. The proteins on the right are using secondary active transport to move potassium into the cell. Active transport is the movement of a substance across a membrane against its concentration gradient. This is usually to accumulate high concentrations of molecules that a cell needs, such as glucose or amino acids. If the process uses chemical energy, such as adenosine triphosphate ATP , it is called primary active transport. Secondary active transport involves the use of an electrochemical gradient , and does not use energy produced in the cell. These carrier proteins have receptors that bind to a specific molecule substrate needing transport. The molecule or ion to be transported the substrate must first bind at a binding site at the carrier molecule, with a certain binding affinity. Following binding, and while the binding site is facing the same way, the carrier will capture or occlude take in and retain the substrate within its molecular structure and cause an internal translocation so that the opening in the protein now faces the other side of the plasma membrane. Facilitated diffusion Facilitated diffusion in cell membrane, showing ion channels left and carrier proteins three on the right. Facilitated diffusion is the passage of molecules or ions across a biological membrane through specific transport proteins and requires no energy input. Facilitated diffusion is used especially in the case of large polar molecules and charged ions; once such ions are dissolved in water they cannot diffuse freely across cell membranes due to the hydrophobic nature of the fatty acid tails of the phospholipids that make up the bilayers. The type of carrier proteins used in facilitated diffusion is slightly different from those used in active transport. They are still transmembrane carrier proteins, but these are gated transmembrane channels, meaning they do not internally translocate, nor require ATP to function. The substrate is taken in one side of the gated carrier, and without using ATP the substrate is released into the cell. They may be used as potential biomarkers Main article: Reverse transport Reverse transport , or transporter reversal, is a phenomenon in which the substrates of a membrane transport protein are moved in the opposite direction to that of their typical movement by the transporter.

Chapter 7 : Summary of Transport Mechanisms

Unlike most ABC transporter proteins that use the energy of ATP hydrolysis to pump substances across the membrane and out of cells, CFTR works as an ion channel that is regulated by both phosphorylation and ATP binding.

Movement, learning, and memory are only a few of the functions that depend on our nervous system. Rapid communication between neurons and modification of neuron-neuron connections involve the interconversion of electrical and chemical signals. The neurotransmitter diffuses across the synapse to the membrane of the neighboring cell and activates ion channels that open transmembrane pores, initiating an electrical signal that will travel along the postsynaptic neuron. To quench the neurotransmitter stimulus, synapses harbor membrane-bound transporters that pump the transmitter out of the synapse and into neighboring cells, allowing the transmitter to be recycled for additional rounds of stimulation. Although neurotransmitter receptors and transporters are linchpins of the nervous system, information on their three-dimensional structures and molecular mechanisms is scarce. Glutamate Receptors Glutamate one of the most common neurotransmitters in the mammalian nervous system and ionotropic glutamate receptors, which are ligand-gated ion channels, are essential to the normal development and function of the nervous system. A major effort in my laboratory is focused on understanding how the atomic structure of glutamate receptors is related to their complex biological functions. To this end, we have been engaged in crystallographic, biophysical, and electrical measurements over the past few years. Our group has determined detailed molecular mechanisms for the actions of full and partial agonists, competitive antagonists, and allosteric modulators on the GluR2-subtype glutamate receptor. Our accomplishments include insights into the subunit stoichiometry and symmetry properties of glutamate receptors and studies of glutamate receptor desensitization, a process for which there had been little understanding at the molecular level. Conformational changes occur in a dimer of the GluR2 ligand-binding core upon activation by agonists such as glutamate or AMPA. In this movie, one subunit is in front, with the domains colored gray and blue. The second subunit is in back, with the domains colored red and purple. At the beginning of the animation, the ligand-binding "clamshells" are in the apo or resting state, and at the end of the animation, the receptor is in the agonist-bound state. The structures of the end states are based on experimentally determined structures; the intermediate conformations are interpolations. The essential conformational changes that lead to opening, or gating, of the ion channel are the closure of each clamshell and the resulting separation of the "linker" regions, which in the intact receptor are coupled to the ion channel domain. See also Sun, Y. Desensitization was first characterized in the acetylcholine receptor, a ligand-gated ion channel that is opened by acetylcholine. In the mids, del Castillo, Katz, and Thesleff found that prolonged application of acetylcholine, as well as other agonists, to the acetylcholine receptor resulted in the diminution of ion flux across the cell membrane. Katz and colleagues postulated that following activation, the receptor entered into an insensitive or desensitized state, one that is refractory to stimulation by acetylcholine or other agonists. Somehow, the agonist-receptor complex had undergone a conformational change that decoupled agonist binding from the opening of the transmembrane ion channel. Many other ligand-gated ion channels have since been shown to undergo agonist-induced desensitization, yet there has been no detailed molecular understanding of desensitization in ligand-gated ion channels. Ionotropic glutamate receptors also undergo desensitization in the presence of agonist, entering the thermodynamically stable, desensitized state on the millisecond timescale. In the case of glutamate receptors, the rate of entry into the desensitized state can help to shape the electrical response in the postsynaptic cell, thus influencing the molecular "memory" at a particular synapse. We have found that glutamate receptors desensitize by altering specific protein-protein contacts. In the absence of glutamate, the interface between glutamate-binding subunits is stable. As soon as glutamate binds, each glutamate-binding subunit undergoes a conformational change that opens the ion channel. Almost as rapid, however, is a rearrangement at the dimer interface that allows the two glutamate-binding subunits to reorient relative to each other, thereby

compensating for the glutamate-induced conformational change that occurs within each subunit. Indeed, the dimer interface is a bit like a clutch in a car: As soon as the protein-protein contacts disengage, the ion channel closes and the receptor enters the desensitized state. Glutamate Transporters Once glutamate activates receptors on the postsynaptic cell, it is cleared from the cleft by high-affinity, sodium-dependent glutamate transporters, integral membrane proteins located on neighboring glial cells and on neurons. These transporters are members of a family of integral membrane transport proteins that includes five eukaryotic glutamate transporters, two eukaryotic neutral amino acid transporters, and a large number of bacterial amino acid and dicarboxylic acid transporters. Eukaryotic members of this transporter family have an essential role in the nervous system and in the heart, kidney, and intestine. Physiological studies have shown that glutamate uptake is coupled to the cotransport of three sodium ions and one proton, and to the countertransport of one potassium ion. Eukaryotic glutamate transporters also possess a thermodynamically uncoupled, glutamate-gated chloride conductance, illuminating their dual roles as secondary transporters and ligand-gated ion channels. Despite the wealth of functional data on glutamate transporters, however, there is little understanding of their three-dimensional architecture or molecular transport mechanism. We recently solved the crystal structure of a eukaryotic glutamate transporter homolog from Pyrococcus horikoshii GltPh. Perhaps the most striking feature of the structure is that the bottom of the hydrophilic basin lies halfway across the membrane bilayer. At the bottom of the basin are three independent binding sites, each cradled by two helical hairpins HP1 and HP2 that reach from opposite sides of the membrane. The depth of the extracellular basin and the immediate proximity of the glutamate-binding sites to the bottom of the basin suggest that glutamate can diffuse, from bulk solution, to binding sites that are halfway across the membrane bilayer. The fact that our structure suggests that glutamate can bind at a nearly diffusion-limited rate agrees with the observation that the quenching of synaptic glutamate by transporters is accomplished by a rapid binding event, on the submillisecond timescale, that is followed by a slow transport process, occurring on the millisecond timescale. The structure of GltPh allowed us to reach a number of important conclusions about this family of transporters. Third, we suggested that HP1 and HP2 are the elements of protein structure that comprise the gates of the transport pathway, and only a modest movement of HP2 is required to render the glutamate-binding site accessible to the extracellular basin. On the basis of our crystal structure, we propose that glutamate transport is achieved by movements of the hairpins, allowing alternating access to either side of the membrane. This research is also supported by the National Institutes of Health. As of May 30, Scientist Profile.

Chapter 8 : Receptors, Ion Channels & Transporters > Pharmacology | Yale School of Medicine

YM90K hydrochloride is a selective AMPA receptor antagonist that delays neuronal death in a global ischemia model and cerebral infarction in a focal ischemia model following postischemic administration.

Chapter 9 : Satinder Singh, PhD > Interdepartmental Neuroscience Program | Yale School of Medicine

A membrane transport protein (or simply transporter) is a membrane protein involved in the movement of ions, small molecules, or macromolecules, such as another protein, across a biological membrane.