DOWNLOAD PDF NEW CONCEPTS IN NEUROTRANSMITTER REGULATION

Chapter 1 : Neurotransmitter - Wikipedia

New Concepts in Neurotransmitter Regulation Proceedings of a Symposium on Drug Abuse and Metabolic Regulation of Neurotransmitters held in La Jolla, Californina, in July

Actions[edit] Neurons form elaborate networks through which nerve impulsesâ€" action potentials â€"travel. Each neuron has as many as 15, connections with neighboring neurons. Neurons do not touch each other except in the case of an electrical synapse through a gap junction ; instead, neurons interact at contact points called synapses: A neuron transports its information by way of a nerve impulse called an action potential. These neurotransmitters are released into the synaptic cleft to bind onto the receptors of the postsynaptic membrane and influence another cell, either in an inhibitory or excitatory way. The next neuron may be connected to many more neurons, and if the total of excitatory influences minus inhibitory influences is great enough, it will also "fire". That is to say, it will create a new action potential at its axon hillock, releasing neurotransmitters and passing on the information to yet another neighboring neuron. Excitatory and inhibitory[edit] A neurotransmitter can influence the function of a neuron through a remarkable number of mechanisms. A neurotransmitter influences trans-membrane ion flow either to increase excitatory or to decrease inhibitory the probability that the cell with which it comes in contact will produce an action potential. Thus, despite the wide variety of synapses, they all convey messages of only these two types, and they are labeled as such. Type I synapses are excitatory in their actions, whereas type II synapses are inhibitory. Each type has a different appearance and is located on different parts of the neurons under its influence. Each neuron receives thousands of excitatory and inhibitory signals every second. In addition, Type I synapses have round synaptic vesicles, whereas the vesicles of type II synapses are flattened. The material on the presynaptic and post-synaptic membranes is denser in a Type I synapse than it is in a type II, and the type I synaptic cleft is wider. The different locations of type I and type II synapses divide a neuron into two zones: From an inhibitory perspective, excitation comes in over the dendrites and spreads to the axon hillock to trigger an action potential. If the message is to be stopped, it is best stopped by applying inhibition on the cell body, close to the axon hillock where the action potential originates. Another way to conceptualize excitatoryâ€"inhibitory interaction is to picture excitation overcoming inhibition. In this "open the gates" strategy, the excitatory message is like a racehorse ready to run down the track, but first the inhibitory starting gate must be removed. Therefore, the effects of a neurotransmitter system depend on the connections of the neurons that use the transmitter, and the chemical properties of the receptors that the transmitter binds to. Here are a few examples of important neurotransmitter actions: Glutamate is used at the great majority of fast excitatory synapses in the brain and spinal cord. It is also used at most synapses that are "modifiable", i. Modifiable synapses are thought to be the main memory-storage elements in the brain. Excessive glutamate release can overstimulate the brain and lead to excitotoxicity causing cell death resulting in seizures or strokes. Acetylcholine was the first neurotransmitter discovered in the peripheral and central nervous systems. It activates skeletal muscles in the somatic nervous system and may either excite or inhibit internal organs in the autonomic system. The paralytic arrow-poison curare acts by blocking transmission at these synapses. Acetylcholine also operates in many regions of the brain, but using different types of receptors , including nicotinic and muscarinic receptors. It functions to regulate appetite, sleep, memory and learning, temperature, mood, behaviour, muscle contraction, and function of the cardiovascular system and endocrine system. It is speculated to have a role in depression, as some depressed patients are seen to have lower concentrations of metabolites of serotonin in their cerebrospinal fluid and brain tissue. It is synthesized from tyrosine. Epinephrine which is also synthesized from tyrosine is released in the adrenal glands and the brainstem. It plays a role in sleep, with ones ability to become and stay alert, and the fight-or-flight response. Histamine works with the central nervous system CNS , specifically the hypothalamus tuberomammillary nucleus and CNS mast cells. Brain neurotransmitter systems [edit] Neurons expressing certain types of neurotransmitters sometimes form distinct systems, where

activation of the system affects large volumes of the brain, called volume transmission. Major neurotransmitter systems include the noradrenaline norepinephrine system, the dopamine system, the serotonin system, and the cholinergic system, among others. Trace amines have a modulatory effect on neurotransmission in monoamine pathways i. Neurotransmitter systems in the brain System Regulated cognitive processes and behaviors Noradrenaline system.

DOWNLOAD PDF NEW CONCEPTS IN NEUROTRANSMITTER REGULATION

Chapter 2 : Regulated neurotransmitter release | The Lasker Foundation

Note: Citations are based on reference standards. However, formatting rules can vary widely between applications and fields of interest or study. The specific requirements or preferences of your reviewing publisher, classroom teacher, institution or organization should be applied.

References Abstract Glutamate is a major excitatory neurotransmitter in the vertebrate central nervous system CNS. Glutamate is released from vesicles that reside at axon terminals of neurons that use this amino acid as a neurotransmitter. Vesicular release is triggered by the arrival of a brief electrical signal the action potential at the presynaptic terminal. Most neurons in the vertebrate CNS, even if they themselves do not use glutamate as a neurotransmitter, are contacted by glutamate presynaptic terminals. Glutamate receptors mediate signalling initiated by glutamate release and are involved in plastic changes in the nervous system. These receptors fall into two classes: Ionotropic glutamate receptor activation on the target cell initiates a brief electrical depolarisation, which if large enough, causes an action potential in the target cell, and the cycle of signalling begins again. Excessive activation of glutamate receptors can cause neurotoxicity. Glutamate is used as a neurotransmitter at the majority of synapses in the vertebrate CNS. Glutamate generally has an excitatory action on target neurons, increasing the probability of action potential firing in the target. Glutamate synapses exhibit remarkable plasticity malleability that may play an important role in memory formation. In excess glutamate can be neurotoxic, acting through the same glutamate receptors that mediate normal signalling. Schematic representation of a glutamate spiny synapse. A functional receptor comprises four of these subunits. M1, M3, and M4 are regions of the protein that traverse the plasma membrane. The darkened regions of the subunit denote extracellular regions of the protein that contribute to glutamate Glu binding. The reentrant loop M2 contributes to the pore region of the receptor channel and allows cations to pass through upon glutamate binding. Unlike the ionotropic receptors, no pore region is present. The binding pocket for glutamate is thought to be associated with a reentrant loop structure M8 reminiscent of the pore region of ionotropic receptors. Journal of Physiology London Danbolt NC Glutamate uptake. Progress in Neurobiology Huettner JE Kainate receptors and synaptic transmission. Annual Review of Pharmacology and Toxicology Trends in Neuroscience Olney JW Brain lesions, obesity, and other disturbances in mice treated with monosodium glutamate. Pharmacology and Therapeutics Handbook of Experimental Pharmacology Trends in Neurosciences 18 2: Nature Reviews Neuroscience Nature Reviews Neuroscience 8: Annual Review of Physiology Yuste R Dendritic spines and distributed circuits.

Chapter 3 : Psychopharmacology - Wikipedia

Read "New Concepts in Neurotransmitter Regulation Proceedings of a Symposium on Drug Abuse and Metabolic Regulation of Neurotransmitters held in La Jolla, Californina, in July " by with Rakuten Kobo.

Scheller Genentech and Thomas C. These advances have provided a molecular framework for understanding some of the most devastating disorders that afflict humans as well as normal functions such as learning and memory. The billions of nerve cells in our brains allow us to savor chocolate, whack a baseball, and imagine traveling at the speed of light. Their exploits tell our hearts to quicken and make us feel as if those same hearts are breaking. Their messages give us eureka moments â€" and let us jump out of the bathtub in response. A biological relay system achieves these feats. Neurotransmission kicks off with an electrical pulse that runs down a nerve cell, or neuron. When that signal reaches the tip, calcium enters the cell. In response, the neuron liberates chemical messengers â€" neurotransmitters â€" which travel to the next neuron and thus pass the baton. In the s, the late Bernard Katz figured out that cells eject neurotransmitters in fixed amounts. Electron-micrographic studies by others illuminated how. Balloon-like containers â€" vesicles â€" each hold set quantities of the chemicals. Calcium incites these lipid-bound sacs to fuse with the membrane that encases the cell, and their contents spill out see Figure. Neurotransmission occurs astonishingly quickly â€" fast enough for a person to pull a hand off a hot burner or dodge an attacking mountain lion. Calcium entry can spark the release of neurotransmitter packages in less than a millisecond. No one knew what drives the vesicles to fuse with the cell membrane or how calcium provokes that event. Focusing first on vesicles, Scheller, then at Stanford University School of Medicine, discovered what would turn out to be an essential piece of the fusion apparatus: When calcium is present, this protein binds to phospholipids, major constituents of membranes. Scheller established that synaptotagmin clutches a brain protein that he named syntaxin. Independently, James Rothman Yale University Lasker Basic Medical Research Award, had been exploring how substances are ferried from one place to another inside cells. In that process, too, transport vesicles deliver their contents by merging their membranes with those of the target compartment. Rothman had proposed that one of the proteins necessary for his experimental system and for fusion in live yeast cells, NSF, attaches to the membrane through a second protein and its as-yet-unidentified collaborators. To nab them, Rothman sought proteins in rat brains that adhere to NSF through its partner. Two separate lines of inquiry thus pointed at the same three molecules. The results suggested that they promote neurotransmitter release by fostering fusion, but provided only indirect evidence. Meanwhile, a clear link to their physiological function had materialized from a different direction. These observations established that the three proteins are vital for neurotransmission. The mechanism of fusion was murky, however, as was the way in which calcium triggers the process. The team also showed that NSF rips apart this assemblage. Scientists later realized that this phenomenon helps recycle the molecular machinery. In the meantime, researchers were defining the precise interactions among these proteins and discerning how the associations might instigate fusion see Figure for current model. The results supported a scenario in which the proteins zipper together, eventually forcing fusion see Figure. Control mechanisms calcify These and other observations were fleshing out the basic mechanism of fusion, but they also highlighted crucial open questions. Uncontrolled, the reaction would result in rampant and constant neurotransmitter release. Although scientists knew that the system does not launch until calcium arrives, the details remained obscure. It was clear, however, that the extremely short time between calcium influx and neurotransmitter discharge would not permit assembly of a multi-protein machine. The device must lie on the brink of its fusion-competent state, waiting for calcium to push it over the edge, presumably by a protein that senses this ion. Perhaps, he speculated, calcium prompts it to facilitate fusion. In , he showed that two regions of synaptotagmin bind calcium, and this property allows it to efficiently grasp phospholipids. In , he generated mice that lack operational synaptotagmin. Although the animals died soon after birth, neurons from their embryos could be studied. He generated a series of mice, each of which carried

a synaptotagmin with altered calcium-binding affinity. Increasing calcium avidity, for instance, decreased by approximately the same amount how much calcium was needed for neurotransmitter release. These results confirmed the notion that synaptotagmin functions as the calcium sensor. Meanwhile, another layer of regulation was surfacing. Subsequent work established that it plays an essential role in calcium-regulated neurotransmitter release. Complexin holds the partially zippered SNARE complex in a form that is poised to trigger fusion, yet inactive until the crucial next step: Calcium binds to synaptotagmin and spurs it to displace complexin, which instantly drives the reaction see Figure. Medical implications Communication within the brain influences how we think and who we are. Defects in the process contribute to schizophrenia, depression, bipolar disorder, and many other pathological conditions. Studies of these illnesses have not yet indicted misbehaving components of the fusion complex itself, but scientists are beginning to uncover connections between this equipment and serious diseases. Their work has revealed the elaborate orchestrations that lie at the crux of our most simple and sophisticated neurobiological activities. A synaptic vesicle-associated integral membrane protein. A synaptic protein implicated in docking of synaptic vesicles at presynaptic active zones. A protein assembly-disassembly pathway in vitro that may correspond to sequential steps of synaptic vesicle docking, activation, and fusion. Protein-protein interactions contributing to the specificity of intracellular vesicular trafficking. Structural organization of the synaptic exocytosis core complex. Key publications of Thomas C. Phospholipid binding by a synaptic vesicle protein homologous to the regulatory region of protein kinase C. A calcium sensor on the synaptic vesicle surface. Cytosolic proteins that regulate SNAP receptor function. Synaptotagmin I functions as a calcium regulator of release probability. The molecular machinery for secretion is conserved from yeast to neurons. The synaptic vesicle cycle: A cascade of protein-protein interactions. Mechanisms of synaptic vesicle exocytosis. Calcium control of neurotransmitter release. See More Award presentation by Eric Kandel We are who we are because of our brain and its ability to acquire and store new information. A synapse has three components: Because of its critical importance for understanding the brain, its role in our capability to learn and to remember, and the many neurological and psychiatric disorders that involve synapses, a molecular understanding of chemical synaptic transmission has been one of the holy grails of neuroscience. The initial steps in addressing this question in the modern era were taken in when Bernard Katz, demonstrated that a chemical transmitter is released from the end of the neuron from a structure called the presynaptic terminal. It is sent not as a single molecule but as a multi-molecular packet, which Katz called a quantum. We now know that each quantum, consisting of a collection of around transmitter molecules, is contained in a little round organelle in the presynaptic terminal that Sanford Palay and George Palade had earlier discovered and called the "synaptic vesicl. For this work Bernard Katz was awarded the Nobel Prize in That these two scientists have accomplished so much is all the more remarkable given the painfully difficult circumstances in which they had to work in the early phases of their careers. Let me begin with Richard Scheller. Richard had the catastrophic misfortune of beginning his scientific career in neuroscience in the years of and by working with Richard Axel and myself. Need I say more? Given how little one of those two knew about the brain and how little the other new about molecules, it is amazing that Scheller survived, much less prospered in science. Beginning in Scheller, then at Stanford, succeeded in characterizing several key proteins necessary for synaptic vesicle fusion with the presynaptic membrane, the prerequisite step for neurotransmitter release. In , Scheller identified the first key vesicle membrane protein, which he termed VAMP, now also known as synaptobrevin. Then in he cloned syntaxin, one of what proved to be two active zone plasma membrane proteins important for neurotransmitter release. Because the two molecules bound to one another Scheller proposed that VAMP, the synaptic vesicle protein, bridges to syntaxin, the plasma membrane protein â€” thereby providing a scaffold onto which the molecular machinery that catalyzes membrane fusion can be assembled. Scheller and Rothman then collaborated and found that the three SNAREs form a stable complex, which can be disassembled when ATP is hydrolyzed by another protein in the system. In , Scheller demonstrated that calcium triggering and the full formation of the SNARE complex are closely associated, thereby providing the first direct evidence that SNARE complex

formation drives the fusion event responsible for neurotransmitter release and the consequent communication between neurons. His life also was no bed of roses. If you know them at all â€" I also need not say more. First, he combined membrane protein biochemistry with molecular biological techniques to identify synaptic vesicle and other key proteins, several in collaboration with Reinhard Jahn. This model was again supported by studies of a mouse model.

Chapter 4 : Glutamate as a Neurotransmitter

New Concepts in Neurotransmitter Regulation: Proceedings of a Symposium on Drug Abuse and Metabolic Regulation of Neurotransmitters held in La Jolla, Californina, in July Softcover reprint of the original 1st ed. Edition.

Alcohol[edit] Alcohol is a depressant , the effects of which may vary according to dosage amount, frequency, and chronicity. As a member of the sedative-hypnotic class, at the lowest doses, the individual feels relaxed and less anxious. In quiet settings, the user may feel drowsy, but in settings with increased sensory stimulation, individuals may feel uninhibited and more confident. High doses of alcohol rapidly consumed may produce amnesia for the events that occur during intoxication. Other effects include reduced coordination, which leads to slurred speech, impaired fine-motor skills, and delayed reaction time. This is because the chemical nature of the substance makes it easy to penetrate into the brain, and it also influences the phospholipid bilayer of neurons. This allows alcohol to have a widespread impact on many normal cell functions and modifies the actions of several neurotransmitter systems. Alcohol inhibits glutamate a major excitatory neurotransmitter in the nervous system neurotransmission by reducing the effectiveness at the NMDA receptor, which is related to memory loss associated with intoxication. It also modulates the function of GABA , a major inhibitory amino acid neurotransmitter. After chronic use, neurons adapt to the change in biochemistry, resulting in a change in pre- and postsynaptic receptor density and second messenger function. They inhibit monoamine oxidase , the enzyme that metabolizes the monoamine neurotransmitters in the presynaptic terminals that are not contained in protective synaptic vesicles. The inhibition of the enzyme increases the amount of neurotransmitter available for release. It increases norepinephrine, dopamine, and 5-HT and thus increases the action of the transmitters at their receptors. MAOIs have been somewhat disfavored because of their reputation for more serious side effects. This increases the availability of 5-HT in the synaptic cleft. Most SSRIs are available generically and are relatively inexpensive. Older antidepressants, such as the TCAs and MAOIs usually require more visits and monitoring, and this may offset the low expense of the drugs. Traditional neuroleptics modify several neurotransmitter systems, but their clinical effectiveness is most likely due to their ability to antagonize dopamine transmission by competitively blocking the receptors or by inhibiting dopamine release. Some of the efficacy of atypical antipsychotics may be due to 5-HT2 antagonism or the blockade of other dopamine receptors. Agents that purely block 5-HT2 or dopamine receptors other than D2 have often failed as effective antipsychotics. This receptor complex is thought to mediate the anxiolytic , sedative, and anticonvulsant actions of the benzodiazepines. Taking these drugs for a long period of time can lead to withdrawal symptoms upon abrupt discontinuation. Onset is the first stage after an individual ingests LSD , psilocybin, or mescaline or smokes dimethyltryptamine the substance. This is followed by a plateau phase, where the subjective sense of time begins to slow and the visual effects increase in intensity. Hallucinogens are classified chemically as either indolamines specifically tryptamines , sharing a common structure with serotonin, or as phenethylamines , which share a common structure with norepinephrine. Both classes of these drugs are agonists at the 5-HT2 receptors; this is thought to be the central component of their hallucinogenic properties. Activation of 5-HT2A may be particularly important for hallucinogenic activity. However, repeated exposure to hallucinogens leads to rapid tolerance, likely through down-regulation of these receptors in specific target cells. Benzodiazepines are still among the most widely prescribed sedative-hypnotics in the United States today. Certain non-benzodiazepine drugs are used as hypnotics as well. Although they lack the chemical structure of the benzodiazepines, their sedative effect is similarly through action on the GABAA receptor. They also have a reputation of being less addictive than benzodiazepines. Melatonin , a naturally-occurring hormone, is often used over the counter OTC to treat insomnia and jet lag. This hormone appears to be excreted by the pineal gland early during the sleep cycle and may contribute to human circadian rhythms. Because OTC melatonin supplements are not subject to careful and consistent manufacturing, more specific melatonin agonists are sometimes preferred. They are used for

their action on melatonin receptors in the suprachiasmatic nucleus , responsible for sleep-wake cycles. Many barbiturates have or had an FDA-approved indication for use as sedative-hypnotics, but have become less widely used because of their limited safety margin in overdose, their potential for dependence, and the degree of central nervous system depression they induce. The amino-acid L-tryptophan is also available OTC, and seems to be free of dependence or abuse liability. However, it is not as powerful as the traditional hypnotics. Because of the possible role of serotonin in sleep patterns, a new generation of 5-HT2 antagonists are in current development as hypnotics. There is commonly increased blood flow to the skin, which leads to sensations of warmth or flushing, and heart rate is also increased. It also frequently induces increased hunger. The first is the "buzz," a brief period of initial responding, where the main effects are lightheadedness or slight dizziness, in addition to possible tingling sensations in the extremities or other parts of the body. The "high" is characterized by feelings of euphoria and exhilaration characterized by mild psychedelia, as well as a sense of disinhibition. Sensory reactions may include the feeling of floating, enhanced visual and auditory perception, visual illusions, or the perception of the slowing of time passage, which are somewhat psychedelic in nature. Both the CB1 receptor and CB2 receptor are found in the brain. The CB2 receptor is also found in the immune system. CB1 is expressed at high densities in the basal ganglia , cerebellum , hippocampus , and cerebral cortex. Receptor activation can inhibit cAMP formation, inhibit voltage-sensitive calcium ion channels, and activate potassium ion channels. Many CB1 receptors are located on axon terminals, where they act to inhibit the release of various neurotransmitters. In combination, these chemical actions work to alter various functions of the central nervous system including the motor system, memory, and various cognitive processes. The ability of opioids both endogenous and exogenous to relieve pain depends on a complex set of neuronal pathways at the spinal cord level, as well as various locations above the spinal cord. Small endorphin neurons in the spinal cord act on receptors to decrease the conduction of pain signals from the spinal cord to higher brain centers. Descending neurons originating in the periaqueductal gray give rise to two pathways that further block pain signals in the spinal cord. The pathways begin in the locus coeruleus noradrenaline and the nucleus of raphe serotonin. Similar to other abused substances, opioid drugs increase dopamine release in the nucleus accumbens. Stimulants[edit] Cocaine is one of the more common stimulants, and is a complex drug that interacts with various neurotransmitter systems. It commonly cause heightened alertness, increased confidence, feelings of exhilaration, reduced fatigue, and a generalized sense of well-being. The effects of cocaine are similar to those of the amphetamines, though cocaine tends to have a shorter duration of effect. Most of the behavioral and physiological actions of cocaine can be explained by its ability to block the reuptake of the two catecholamines , dopamine and norepinephrine, as well as serotonin. Cocaine binds to transporters that normally clear these transmitters from the synaptic cleft, inhibiting their function. This leads to increased levels of neurotransmitter in the cleft and transmission at the synapses. Various forms of amphetamine are commonly used to treat the symptoms of attention deficit hyperactivity disorder ADHD and narcolepsy , or are used recreationally. Amphetamine and methamphetamine are indirect agonists of the catecholaminergic systems. They block catecholamine reuptake, in addition to releasing catecholamines from nerve terminals. There is evidence that dopamine receptors play a central role in the behavioral responses of animals to cocaine, amphetamines, and other psychostimulant drugs. One action causes the dopamine molecules to be released from inside the vesicles into the cytoplasm of the nerve terminal, which are then transported outside by the mesolimbic dopamine pathway to the nucleus accumbens. This plays a key role in the rewarding and reinforcing effects of cocaine and amphetamine in animals, and is the primary mechanism for amphetamine dependence. Psychoactive substances and Psychiatric medication In psychopharmacology, researchers are interested in any substance that crosses the bloodâ€”brain barrier and thus has an effect on behavior, mood or cognition. Drugs are researched for their physiochemical properties, physical side effects , and psychological side effects. Researchers in psychopharmacology study a variety of different psychoactive substances that include alcohol, cannabinoids, club drugs , psychedelics, opiates, nicotine , caffeine , psychomotor stimulants , inhalants , and anabolic-androgenic steroids. They also study drugs used in the

treatment of affective and anxiety disorders, as well as schizophrenia. Clinical studies are often very specific, typically beginning with animal testing, and ending with human testing. In the human testing phase, there is often a group of subjects, one group is given a placebo, and the other is administered a carefully measured therapeutic dose of the drug in question. After all of the testing is completed, the drug is proposed to the concerned regulatory authority e. FDA , and is either commercially introduced to the public via prescription , or deemed safe enough for over the counter sale. Though particular drugs are prescribed for specific symptoms or syndromes, they are usually not specific to the treatment of any single mental disorder. Because of their ability to modify the behavior of even the most disturbed patients, the antipsychotic, antianxiety, and antidepressant agents have greatly affected the management of the hospitalized mentally ill, enabling hospital staff to devote more of their attention to therapeutic efforts and enabling many patients to lead relatively normal lives outside of the hospital. The antidepressant bupropion is then prescribed to increase perceived energy levels and assertiveness while diminishing the need for sleep. The antihypertensive compound propranolol is sometimes chosen to eliminate the discomfort of day-to-day anxiety. Fluoxetine in nondepressed people can produce a feeling of generalized well-being. Pramipexole , a treatment for restless leg syndrome, can dramatically increase libido in women. These and other off-label lifestyle applications of medications are not uncommon. Although occasionally reported in the medical literature no guidelines for such usage have been developed.