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2000 Nobel Prize Medicine

Carlsson, Greengard and Kandel received the Nobel Prize in Medicine or Physiology in 2000 for their discoveries concerning the signal transduction in nervous system.

Arvid Carlsson was awarded the Nobel Prize for his discovery of the neurotransmitter dopamine and its clinical relevance to a condition known as Parkinson's disease. Paul Greengard was awarded the Nobel Prize for his contributions on the mechanism of action of dopamine and other neurotransmitters. Lastly, Eric Kandel was rewarded for his discovery of the molecular mechanisms in the formation of short-term and long-term memory.

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Basics of Signal Transduction in Nervous System

The human nervous system is made of billions of receptors, neurons and effectors. The neuron is basically composed of three parts, the dendrites which receive the incoming information, the soma or the cell body which processes the received information and the axon which sends out the information to another neurons or effectors.

The information from one neuron is passed on to another neuron or to an effector through small special gaps or spaces called synapses.

A neuron can have thousands of such special gaps or synapses with other neurons. These gaps or synapses are bridged by chemicals known as neurotransmitters. These are chemicals that are synthesized in the neurons, stored in synaptic vesicles, released in the synapses; transfer the information by binding to its receptors in the other neuron to start a cascade of events leading to a specific response.

The Winners

Arvid Carlsson was born on the 25th of January 1923 in Uppsala, Sweden. His family had a very strong orientation to the humanities but at a young age, he thought that science is more useful than arts. Because of this line of reasoning, he entered Lund University to take up medicine in 1941. He earned his M.D. in 1951 due to the effects of WWII. He then became of professor in Lund University and in 1959, a professor in the University of Gothenburg. In 1957, despite the worldwide accepted fact that dopamine was only a precursor of norepinephrine, he proved the dopamine was a neurotransmitter in itself and not just a precursor of other neurotransmitters.

Paul Greengard was born on the 11th of 1925 in New York City. It was not a completely delightful day for their family since his mother died while giving birth to him. Greengard attended public schools in Brooklyn and Queens. After the Second World War, he attended Hamilton College in New York and majored in mathematics and physics. He then developed an interest in Biophysics and participated in a research headed by Detlev W. Bronk who used electrophysiological techniques to study nerve function. In 1953, he earned his Ph.D. in John Hopkins University. From 1953-1959 he conducted postdoctoral studies in biochemistry at University of London, Cambridge University, and National Institute for Medical Research, England.

Eric Kandel was born on the 7th of November 1929 in Vienna, Austria. He entered Harvard University and majored in Literature and History. He then became interested in learning and memory despite the fact that Harvard was dominated by B.F. Skinner, a well-known Psychologist of that time who pioneered on experimental conditioning. In 1952, he entered New York University Medical School and his fascination to the human mind became firmer. In 1960, he became a resident in Psychiatry in Harvard Medical School and a staff Psychiatrist in 1964.

Discovery of Dopamine as a Neurotransmitter and Its Relevance to Parkinson's Disease

In the 1950's, scientists thought that dopamine is just a precursor of norepinephrine or noradrenaline. This line of thinking was completely changed when Arvid Carlsson developed an assay used to measure the amount of dopamine contained in specific tissue samples. His research found that dopamine was highly concentrated in an area of the brain called basal ganglia, especially in substantia nigra. Furthermore, he found that the level of dopamine in this structure was higher compared to its noradrenaline content. These results led him to a

conclusion that dopamine in itself is a neurotransmitter and not just a precursor other neurotransmitters.

Basal Ganglia, the part of the brain with high dopamine content, is of particular importance in the control of fine motor behavior. In his succeeding experiments, he introduced reserpine, a chemical used to deplete the storage the neurotransmitters including dopamine, to different animals. He noted that the animals showed inability to perform spontaneous movements, presumably due to the depletion of dopamine. Carlsson showed that the animals which lost normal motor behavior, if subjected to L-dopa which is a precursor of dopamine, resumed normal movements which are associated with normal levels of dopamine in the brain. There is also a human condition characterized by tremors, rigidity and reduced ability for spontaneous movements, similar to what the animals displayed in the study. This condition is called Parkinson's disease. It is caused by the degradation of dopaminergic neurons in the basal ganglia.

Discovery of Mechanisms Involved in Slow Synaptic Transmission

There are two types of synaptic transmission: fast synaptic transmission that lasts for a short duration with an electrical nature and slow synaptic transmission which lasts for a longer duration with a chemical nature. Slow signal transduction in nervous system involves an action potential that causes the secretion of a chemical substance called neurotransmitter by the presynaptic cell. The secreted neurotransmitter then binds to its specific receptor on the postsynaptic membrane of the other neuron to initiate a cascade of events leading to a specific response.

Paul Greengard showed that slow synaptic transmission involved phosphorylation of certain proteins, particularly in synapses. He demonstrated that when dopamine stimulates its receptor in the postsynaptic membrane, it causes an increase in cyclic AMP or cAMP which is a secondary messenger. The increase in intracellular cAMP levels causes an increase in Protein Kinase A levels or PKA. The high intracellular PKA level causes phosphorylation of certain proteins in the nerve cell. Phosphorylation is a process wherein a phosphate group is added to the structure of the protein thus changing its shape and function.

Discovery of Model System for Learning

Signal transduction in nervous system is highly dependent on the plasticity of the synapses. Synaptic plasticity is described as the ability of the synapses to undergo alterations. It involves restructuring of synapses for long-term changes, and depends partly on phosphorylation of proteins, especially synapses. In the research conducted by Kandel, he was able to demonstrate that short-term and long-term memories are located in the synapse and are mostly governed by synaptic plasticity. He also showed that changes in the shape and function of the synapse are central to learning and memory.

He used the simple protective reflex that protects the gills of a sea slug, *Aplysia*, to study its basic learning mechanisms. Kandel noted that some stimuli resulted in the amplification or strengthening of the protective reflex of the sea slug. He observed that this reflex amplification endured for days, even weeks after stimulation and was thus considered a form of learning.

Kandel was also able to differentiate the mechanisms behind long-term memory and short-term memory. He showed that weaker stimuli cause the development of short-term memory. The mechanism behind the development of short-term memory involves an alteration in the calcium channels causing an increase in intracellular calcium levels in the presynaptic membrane. This triggers an increase in the release of neurotransmitters into the synapse causing an amplification of the reflex. On the other hand, a stronger stimuli cause the development of long-term memory. Stronger stimuli cause an increase in cAMP levels which increases intracellular PKA. These signals reach the nucleus of the nerve which leads to an increase in the synthesis of certain proteins. If the synthesis of these proteins is inhibited, long-term memory is blocked but short-term memory is not affected.

Clinical Relevance

The discovery regarding signal transduction in nervous system ^[1] triggered a lot of researches that led to an understanding of the mechanisms involved in several neurological disorders and consequently helped in the development of new drugs and therapies for the treatment of these disorders. Researches targeting the cure of Parkinson's disease and the loss of learning or memory are main results of this discovery. So far, there is no absolute cure for these diseases and any progress made in this area is a significant step forward towards the amelioration of human sufferings due to these neurological disorders.

Hopefully, future research in this area lead to the development of new drugs and therapies that can serve as permanent and absolute cure for these diseases.

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Links

[1] <http://www.medicinenet.com/script/main/art.asp?articlekey=14864>