

Nobel prize awarded for research into the nervous system, memory and mood

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This year's Nobel Prize for Physiology or Medicine was awarded to three prominent scientists—Arvid Carlsson, Paul Greengard and Eric Kandel—for their ground-breaking work in unravelling the functioning of the brain and nervous system. Their discoveries have deepened our understanding of how nerve cell signals are processed, and hence how signal disturbances in nerves give rise to neurological and psychiatric diseases such as Parkinson's Disease, depression and schizophrenia. This research has already led to treatments for these debilitating conditions and may bring scientists closer to finding cures.

Carlsson, Greengard and Kandel, all in their seventies, have worked for decades to reveal details of how a message from one nerve cell is transmitted to another via different chemicals—known as neurotransmitters. It has been understood since the 1920s and 1930s that nerve cells communicate via electric signal as well as by chemicals. The process of electrical signalling is quite well understood. Chemical signalling, however, is far more complex and involves a number of different neurotransmitters and biochemical pathways.

Carlsson, from the University of Gothenburg in Sweden, has worked in the field of nerve transmission since the 1950s. His research focused on the important neurotransmitter dopamine which can, by “exciting” or “inhibiting” certain nerve cells or neurons, affect bodily functions such as movement.

Carlsson revealed that dopamine was concentrated in a specific part of the brain called the “basal ganglia” that is associated with voluntary motor behaviour, or voluntary movement. In patients suffering Parkinson's Disease, the dopamine-producing nerve cells in the basal ganglia die, causing the disease's typical symptoms: tremors, slowness of voluntary movement,

difficulty with balance and muscle rigidity.

In Carlsson's experiments, animals were given a substance which blocked the storage of several neurotransmitters. The animals were unable to perform spontaneous movements. He then treated them with L-DOPA, a chemical precursor that is transformed to dopamine in the brain, and they resumed normal behaviour. L-DOPA was developed as a drug for Parkinson's Disease and is still the most important means of treating the disease.

Greengard, based at New York's Rockefeller University, revealed the complex ways in which neurotransmitters like dopamine, noradrenaline and serotonin function across the gaps between nerve cells known as synapses. His work, which began at the Johns Hopkins biophysics laboratory in 1948, was crucial to understanding the effects of certain drugs on diseases such as schizophrenia.

Prior to Greengard's discoveries, the use of anti-psychotic medications to treat schizophrenia was a case of trial and error—no one could say why they were effective. Greengard provided the missing link by working out the details of nerve cell communication, compiling what he termed “the biochemical inventory”. As Greengard said: “If you want to understand how nerve cells function—and why they falter—you have to understand their biochemistry.”

Neurotransmitters like dopamine send their messages through what is known as “slow synaptic transmission”. Once they are released, their effect on other nerve cells can last from seconds to hours. This particular form of transmission is responsible for a number of important nervous functions, including alertness and mood and indirectly affects speech, movement and sensory perception.

Greengard showed that chemicals such as dopamine

are transmitted between cells by a complex chain of chemical reactions known as “protein phosphorylation”. Once chemicals such as dopamine are released into a nerve cell, certain “key proteins” within the cell become phosphorylated—have phosphate added to them. This chemical change determines whether a particular nerve cell will react or not. Greengard's painstaking work has led to a plethora of discoveries by other scientists who have uncovered other molecular pathways which activate or deactivate certain functions of the brain.

The third Nobel laureate, Kandel, currently University Professor at the Center for Neurobiology and Behavior at Columbia University, extended Greengard's work. Originally born in Austria, Kandel fled the Nazis in 1939 and has since worked in the US. His research has been into the molecular mechanisms involved in the formation of memories.

Realising that the nervous systems of mammals were too complex to serve as a starting point for investigating memory, Kandel conducted a series of experiments on an organism with a simple nervous system—the giant marine slug *Aplysia*, which measures 30 centimetres from head to tail. The slug has a simple protective reflex system—when a particular area was prodded, the gills would withdraw. By examining the operation of this reflex in detail, Kandel was able to get an insight into short- and long-term memory.

When *Aplysia* received a weak stimuli in the form of short prods, a series of interconnected chemical changes—a chemical pathway—would follow within the nerve cells. The neurotransmitter serotonin was released that would activate “protein kinase A” or PKA. In turn, PKA, modified other proteins producing a strong electrical connection between neurons that would last from several minutes to hours. There was, however, no long-term change as the proteins would return to their normal state.

But when the slug was continually prodded, it would stop responding completely and the effect would last for weeks. Kandel found that for this long-term memory to occur, certain genes needed to be “turned on” or activated through the release of a protein known as CREB 1. Once the genes were turned on, certain proteins would be released, which reshaped the end of the nerve cell or synapse and changed how it functioned for a lengthy period of time. Other

experiments have confirmed that long-term memory cannot develop unless the particular genes in the nerve cells are switched on to produce these new proteins. If that process is blocked, nerve cells are only capable of short-term memory.

CREB-1 is also linked to long-term memory in other animals. For example, when a chemical similar to CREB-1 was given to flies, they were able to learn skills that researchers term “photographic memory” in one training session compared to the 10 sessions normally needed. Furthermore, mice with a defect in their ability to produce CREB-1 were unable to remember their way through a maze for longer than a day.

Kandel's work provides an important clue to understanding how complex memory images are stored in the human brain. Scientists hope to uncover the chemical pathways that cause different types of memory by investigating the operation of certain genes in nerve cells. In this way, they eventually hope to be able to map functions to different parts of the brain. Kandel's findings may also lead to the discovery of new drugs to improve the memory of patients suffering from dementia.

The discoveries of Carlsson, Greengard and Kandel have provided an insight into the intricate chemical and electrical processes that lie behind the functioning of the nervous system. Their research has begun to reveal the physiological foundations of complex human phenomena such as mood and memory that condition the way in which individuals interact with the physical and social environment. In doing so they have opened the way for developing new treatments for a number of debilitating nervous disorders.



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