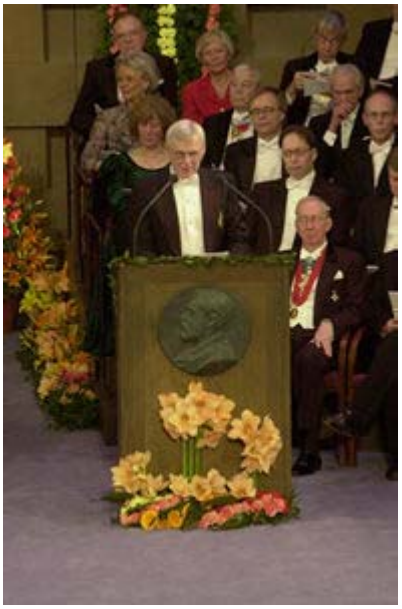
The Nobel Prize in Physiology or Medicine 2000

Presentation Speech

Presentation Speech by Professor Urban Ungerstedt of the Nobel Committee at Karolinska Institutet, December 10, 2000.

Translation of the Swedish text.



Professor Urban Ungerstedt delivering the Presentation Speech for the 2000 Nobel Prize in Physiology or Medicine at the Stockholm Concert Hall.

Photo: Hans Mehlin

Your Majesties, Your Royal Highnesses, Ladies and Gentlemen,

This year's Nobel Prize in Physiology or Medicine concerns the most complex structure in the universe that we know of - the human brain. It consists of 100 billion nerve cells, which is the same number of cells as the total number of human beings that have ever lived on this earth.

We talk about the "Internet revolution"; 35 million Internet users who communicate now and then - what is that compared to the nerve cells we all carry within ourselves! 100 billion nerve cells that communicate continuously.

It is this communication, "signal transduction in the nervous system," which is the subject of this year's Nobel Prize. A single nerve cell forms thousands of contact points, so-called synapses, with other nerve cells. In these synapses the nerve cells communicate by chemistry; one cell releases a transmitter, which reaches the other cell.

Professor Arvid Carlsson proved that dopamine is such a transmitter. The general belief was that dopamine was a precursor of other transmitters and of little functional importance. However, Professor Carlsson was able to show that dopamine existed in specific parts of the brain and concluded that it was a transmitter in its own right.

He then used a naturally occurring substance, reserpine, which empties the dopamine from the nerves, and found that the animals lost their ability to move. He realized that it must be possible to restore the dopamine levels with L-DOPA, a precursor of dopamine. In a conclusive, dramatic experiment he showed that the animals regained their ability to move when he gave them L-DOPA.

Reserpine had depleted dopamine and had given the animals the symptoms of Parkinson's disease, that is, rigidity and inability to move and react to stimuli in the environment. When the animals were given L-DOPA, dopamine was produced again in their brains. In this way the idea of treating Parkinson patients with L-DOPA was born. This enables millions of patients around the world to live a normal life.

Professor Paul Greengard showed what happens when dopamine and other similar transmitters stimulate a nerve cell. Receptors on the cell surface activate enzymes in the cell wall, which starts the production of second messengers. These messengers travel into the cell and activate a protein kinase, which starts to bind phosphate groups to other proteins, in this way altering their function. This leads, for example, to the opening of ion channels in the cell membrane and a change in the electrical activity of the cell.

Professor Greengard then showed that dopamine and other transmitters affect a central regulatory protein, which has been called DARPP-32. Like the conductor of an orchestra, it tells other proteins when and how to be activated.

This so-called "slow synaptic transmission" controls our movements and also those processes in the brain that elicit emotions or react to addictive drugs such as cocaine,

amphetamine and heroin.

Professor Eric Kandel showed that transmitters of the same type as studied by Arvid Carlsson, via the protein kinases characterized by Paul Greengard, are involved in the most advanced functions of the nervous system such as the ability to form memories.

Imagine how difficult or impossible it must be to study how memory is formed in a human brain with 100 billion nerve cells. Eric Kandel, therefore, did something which is classical in all natural science: He chose to study a simpler model system, a sea slug, Aplysia, which has 20,000 nerve cells. He did it with the conviction that even primitive animals must learn in order to survive.

The sea slug has a withdrawal reflex protecting its gills. If they are touched repeatedly, they react less and less - just as human beings do when subjected to an unexpected touch. If, on the other hand, the touch is forceful the reflex is amplified and becomes stronger and stronger.

The habituation or amplification effect lasts only for a few minutes. One may say that the sea slug exhibits a short-term memory. If the forceful stimulus is repeated several times, the sensitization may remain for weeks, that is, the sea slug develops a long-term memory.

Professor Kandel was able to show that habituation to touching was due to changes in the synapse, the contact point between the nerve cells. During habituation less and less transmitter was released.

The forceful stimulus that formed the long-term memory worked in a completely different way. Second messengers activated protein kinases that entered the cell nucleus and started the production of new proteins. This, in turn, brought about a change in the form and function of the synapse. What we call memory is, thus, elicited by direct changes in the billion of synapses that form the contact points between the nerve cells.

I am convinced that you and I will remember this Nobel ceremony for many years. This is because of the dopamine which Arvid Carlsson discovered, enabling the brain to react to what we see and hear; the second messengers that Paul Greengard described, carrying the signals into the nerve cell; and the memory functions that Eric Kandel found to be due to changes in the very form and function of the synapses.

Dear Arvid Carlsson, Paul Greengard and Eric Kandel. Your discoveries concerning "signal transduction in the nervous system" have truly changed our understanding of brain function. From Arvid Carlsson's research we now know that Parkinson's disease is due to failure in synaptic release of dopamine. We know that we can substitute the lost function by a simple molecule, L-DOPA, which replenishes the emptied stores of dopamine and in this way, give millions of humans a better life.

We know from Paul Greengard's work how this is brought about. How second

messengers activate protein kinases leading to changes in cellular reactions. We begin to see how phosphorylation plays a central part in the very orchestration of the different transmitter inputs to the nerve cells.

Finally, Eric Kandel's work has shown us how these transmitters, through second transmitters and protein phosphorylation, create short- and long-term memory, forming the very basis for our ability to exist and interact meaningfully in our world.

On behalf of the Nobel Assembly at Karolinska Institutet, I wish to convey our warmest congratulations and I ask you to step forward to receive the Nobel Prize from the hands of His Majesty the King.