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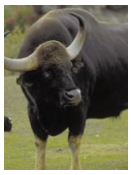

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Rare ox cloned and implanted in cow surrogate mother
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Medicine Nobel goes to raiders of the brain's chemical secrets

Alison Abbott

In 1990, the film *Awakenings* won Robert De Niro an Oscar nomination for his portrayal of a patient with a severe form of Parkinson's disease, who was released from his trance-like state by the drug L-DOPA. This week, the pharmacologist who made the treatment possible is one of three researchers to win the Nobel Prize in Physiology or Medicine for their pioneering discoveries about how signals are transmitted between nerve cells.

Arvid Carlsson, of the University of Gothenburg in Sweden, is honoured for showing that dopamine is a neurotransmitter in the brain, and that lack of this chemical causes the symptoms, such as impaired movement, seen in Parkinson's disease. He also showed that both the chemical deficiency and clinical symptoms can be reversed — at least temporarily — by L-DOPA, a dopamine precursor that is converted into the neurotransmitter in the brain.

Carlsson's discoveries laid the foundations for the work of the US neuroscientists Paul Greengard and Eric Kandel, who share the prize. Studying dopamine-releasing nerve cells, Greengard unravelled the cascade of molecular events needed for a signal to pass across the synapses, the junctions between nerve cells. Kandel showed that changes in synaptic function are essential for learning and memory.

In a series of experiments in the 1950s, Carlsson showed that dopamine was concentrated in parts of the brain involved in movement control. He noted that reserpine, a natural alkaloid used at that time to treat schizophrenia, depleted dopamine stores in the presynaptic neurons. Rabbits treated with reserpine became incapable of voluntary movement, but they recovered when they were given L-DOPA, which compensated for the depleted dopamine.

Carlsson realized that the 'frozen' rabbits were similar to patients with severe Parkinson's, and within a few years L-DOPA was in clinical use. Carlsson also showed that drugs to treat schizophrenia work by blocking dopamine receptors on the surface of postsynaptic nerve cells, stopping the signal from being passed on. Overall, his work has revealed how important dopamine balance is in the brain: too much results in psychosis, too little causes motor disorders.

EPA

Nervous Nobels: Kandel (left), Greengard (middle) and Carlsson.

Greengard, now at Rockefeller University in New York, acknowledges his debt to Carlsson. "One of the reasons I started working on dopamine transmission was because Carlsson had shown the role of dopamine in schizophrenia and shown that antischizophrenic drugs work by disrupting dopamine signalling," he told *Nature*, shortly after learning of his award.

In the 1960s, Greengard began to focus on what happens after dopamine binds to receptors on the surface of postsynaptic neurons. It was known that when some hormones bind to their receptors there is an increase in the level of the second messenger, cyclic AMP. This activates enzymes known as kinases, which add phosphate groups to various proteins, modifying their functions.

"Greengard had the vision and courage to take these concepts of second-messenger signalling processes to the brain — a very tough playground," says Alfred Gilman of the University of Texas Southwestern Medical Center in Dallas, who shared the 1994 Nobel prize for his work on signal transduction within cells.

Over the years, Greengard showed that dopamine, as well as other neurotransmitters, provokes a complicated cascade of phosphorylation and dephosphorylation events. In particular, he found that a protein called DARPP-32 plays a fundamental role in regulating the phosphorylation states of many of the proteins in dopamine signalling pathways. He also investigated interactions between different pathways. "The more complicated the interaction between different signalling pathways becomes, the more intriguing it all becomes," Greengard says.

Eric Kandel of Columbia University in New York studied the cellular processes involved in learning and memory using the sea slug *Aplysia* as a model. *Aplysia* does not have much to remember — but it does have a reflex to protect its gills. Kandel found that some stimuli amplified this reflex for days or weeks. This 'learning', he showed, arises from an increase in neurotransmitter release at synapses connecting the sensory nerve cells to those that activate the muscles involved in the reflex. This rise is mediated by protein phosphorylation mechanisms similar to those studied by Greengard.

Kandel elucidated the cellular basis of short- and long-term memory in *Aplysia* and has extended the studies to mammals. "He has been a leader in the field and it is appropriate that he is rewarded," says Tim Bliss, head of neurophysiology at the National Institute for Medical Research in London, who in the early 1970s described a molecular mechanism for learning and memory known as long-term potentiation (LTP). "Kandel created the intellectual climate in which LTP could be studied, by showing that changes in synaptic efficiency could lead to changes in behaviour," Bliss adds. ■

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