The Nobel Prize in Physiology or Medicine 1963

Presentation Speech

Presentation Speech by Professor R. Granit, member of the Nobel Committee for Physiology or Medicine of the Royal Caroline Institute

Your Majesties, Your Royal Highnesses, Ladies and Gentlemen.

This year's Nobel Prize in Physiology or Medicine concerns the basic processes underlying the nervous mechanisms of control and the communication between nerve cells. When physiologists, in the manner of physicists and chemists, have attempted to define unitary events, they have encountered the nerve cell and the nerve fibre. The impulse in the fibre is an electrical pulse which lasts 1/1000 second. In series of such pulses the nerve cells communicate with each other and give orders to muscles and glands in the body. The results of the Nobel Laureates deal with the nature of the nerve impulse itself and with the electrical changes that it causes at the bodies of nerve cells, in particular the two fundamental events called excitation and inhibition respectively. Their methods are based on electronics. The electrical processes have been recorded with microelectrodes, amplified about a million times, and then displayed on the screen of a cathode ray tube.

The new developments began with an experiment in 1939 by Hodgkin and Huxley. This was intended to check the classical theory of Bernstein according to which the nerve impulse is a travelling permeability leak shunting inside to outside across the fibre membrane. Under these circumstances the impulse at its best could only develop an amount of potential change corresponding to that of the inside of the fibre, as measured across its membrane, provided that this potential actually could be recorded between inside and outside of the fibre. They succeeded in carrying out this experiment with the squid giant nerve fibre into which it was possible to insert an electrode. The impulse was found to deliver an amount of potential change which exceeded by one third that of the inside which is determined by a potassium concentration battery.

After the second World War Hodgkin and Huxley returned to their unexpected result and decided to test a theory which in 1904 had been propounded by Ernest Overton, later professor in pharmacology at Lund. His theory suggested that the nerve impulse involved an exchange between sodium ions from the outside and potassium ions from the inside of the fibre.

School physics has taught us, that current intensity, resistance and potential are related to each other in the manner defined by Ohm's simple law. This is an equation in which three quantities are unknown and so the experimental solution requires knowledge of two of them in order to calculate the third. To this end Hodgkin and Huxley introduced two electrodes into the giant nerve fibre of the squid. One served to clamp the voltage in predetermined steps, the other to measure the current produced during activity. Calculation gave the third quantity, the resistance of the membrane, whose inverse value, the permeability or conductance, was the one which the experiments were designed to measure.

When next the experiment was carried out with the excised nerve in solutions of different ionic concentrations, it was found that the ionic current during impulse activity depended upon two transient and successive changes of permeability both of which were selective. The rising phase of the impulse corresponded to a sodium permeability which after about half a millisecond was replaced by a potassium permeability in the falling phase. During the rising phase positive sodium ions flowed into the nerve from the outside and produced the overshoot of potential by which the impulse exceeded that of the nerve's potassium battery. In the falling phase potassium ions from the inside migrated outwards. Both phases were measured quantitatively and described in a formula which, inserted in a computer, made it possible to predict a number of known and unknown fundamental attributes of excitability, inasmuch as these depend upon the ionic events discovered.

Hodgkin and Huxley's ionic theory of the nerve impulse embodies principles, applicable also to the impulses in muscles, including the electrocardiogram of the heart muscle, a fact of clinical significance. It has likewise proved to be valid for vertebrate nerve fibres, as demonstrated by Dr. Bernhard Frankenhaeuser of the Nobel Institute for Neurophysiology in Stockholm. Their discovery is a milestone on the road towards the understanding of the nature of excitability.

Sir John Eccles' discoveries concern the electrical changes which the nerve impulses elicit when they reach another nerve cell. In this experiment the microelectrode, with a tip of less than 1/1,000 mm, is placed, for instance, in a so-called motoneurone in the spinal cord. These motor cells have a diameter between 40 and 60 thousandth of a mm. The arriving impulse produces excitation or inhibition in the motor cell, because the terminals of the nerve fibre are connected to excitatory or inhibitory chemical mechanisms at the cell membrane. These are called synaptic mechanisms because the points of contact are known as *synapses*, a term introduced by Sherrington. There are two kinds of synapses, one excitatory, the other inhibitory. If the arriving impulse is connected to excitatory synapses the response of the cell is *yes, i. e.* excitability increases, *vice versa* the inhibitory synapses make the cell respond with a *no*, a diminution of excitability. Eccles has shown how excitation and inhibition are expressed by changes of membrane potential.

When the response is sufficiently strong to cause excitation, the membrane potential decreases until a value is reached at which the cell fires off an impulse, the sodium impulse we have spoken of. This impulse travels through the nerve fibre of the cell and in our example causes contraction in a muscle. Obviously a cell may also send impulses to another cell at whose membrane the synaptic processes repeat themselves with plus or minus sign, as the case may be.

A cell engaged in activity may be influenced by impulses reaching inhibitory synapses. In this case the membrane potential increases and, as a consequence, the impulse discharge is inhibited. Thus excitation and inhibition correspond to ionic currents which push the membrane potential in opposite directions.

The nerve cells are provided with thousands of synapses which correspond to terminals of fibres originating in sense organs or other nerve cells. The sum total of synaptic processes determines the state of balance between excitation and inhibition in which the integrated messages of nerve cells find expression and the code of impulses its interpretation.

Sir John, Professor Hodgkin, Professor Huxley. The visual and acoustic impressions we have of this festive occasion with its great traditions in the history of science, our very thinking itself, our talk, our reading, are founded on processes within the central nervous system, that is, on the language of electrical nerve impulses and on the responses of nerve cells engaged in replying to it at synapses. By elucidating the nature of the unitary electrical events in the peripheral and central nervous system you have brought understanding of nervous action to a level of clarity which your contemporaries did not expect to witness in their life time.

It is with great pleasure and satisfaction that I now congratulate you on behalf of the Royal Caroline Institute.

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