NOBEL LECTURES

PHYSIOLOGY OR MEDICINE

生理学或医学诺贝尔奖讲演集

1963-1970

World Scientific
世界图书出版公司

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INCLUDING PRESENTATION SPEECHES
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PHYSIOLOGY
OR
MEDICINE

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世界图书出版公司

Published for the Nobel Foundation in 1999 by

World Scientific Publishing Co. Pte. Ltd.
P O Box 128, Farrer Road, Singapore 912805
USA office: Suite 1B, 1060 Main Street, River Edge, NJ 07661
UK office: 57 Shelton Street, Covent Garden, London WC2H 9HE

NOBEL LECTURES IN PHYSIOLOGY OR MEDICINE (1963–1970)

ISBN 981-02-3412-0

书　　名：Nobel Lectures in Physiology or Medicine 1963-1970
中 译 名：生理学或医学诺贝尔讲演集 1963-1970
出 版 者：世界图书出版公司北京公司
印 刷 者：北京世图印刷厂
发　　行：世界图书出版公司北京公司 (北京朝内大街 137 号　100010)
联系电话：010-64015659, 64038347
电子信箱：kjsk@vip.sina.com
开　　本：24
印　　张：22
出版年代：2003 年 10 月
书　　号：7-5062-6564-8/ Q・13
版权登记：图字:01-2003-6296
定　　价：68.00 元

Foreword

Since 1901 the Nobel Foundation has published annually *Les Prix Nobel* with reports from the Nobel award ceremonies in Stockholm and Oslo as well as the biographies and Nobel lectures of the Laureates. In order to make the lectures available to people with special interests in the different prize fields the Foundation gave Elsevier Publishing Company the right to publish in English the lectures for 1901–1970, which were published in 1964–1972 through the following volumes:

Physics 1901–1970	4 vols.
Chemistry 1901–1970	4 vols.
Physiology or Medicine 1901–1970	4 vols.
Literature 1901–1967	1 vol.
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Since the Elsevier series has been out of print for many years the Nobel Foundation has given World Scientific Publishing Company the right to publish these Nobel lectures, biographies and presentation speeches. The Nobel Foundation is very pleased that the intellectual and spiritual message to the world laid down in the laureates' lectures will, thanks to the efforts of World Scientific, reach new readers all over the world.

Bengt Samuelsson
Chairman of the Board

Michael Sohlman
Executive Director

Stockholm, March 1998

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ANDREW FIELDING HUXLEY

«for their discoveries concerning the ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane»

Physiology or Medicine 1963

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.

JOHN CAREW ECCLES

The ionic mechanism of postsynaptic inhibition

Nobel Lecture, December 11, 1963

The body and dendrites of a nerve cell are specialized for the reception and integration of information which is conveyed as impulses that are fired from other nerve cells along their axons. In this diagrammatic drawing of a nerve cell (Fig. 1A) it is seen that impinging on its surface are numerous small knob-like endings of fine fibres which are, in fact, the terminal branches of axons from other nerve cells. Communication between nerve cells occurs at these numerous areas of close contact or *synapses*, the name first applied to them by Sherrington, who laid the foundations of what is often called synaptology. We owe to Dale and Loewi the concept that transmission across synapses is effected by the secretion of minute amounts of specific chemical substances that act across the synapse. The cable-like transmission of impulses over the surfaces of nerve cells and their axons ceases abruptly at the synaptic contact between cells, but may begin again on the other side of the synapse.

The high resolving power of electron-microscopy gives essential information on those structural features of synapses that are specially concerned with this chemical phase of transmission. For example in Fig. 1B, C, we can see the membrane, about 70 Å thick, that encloses the expanded axonal terminal or *synaptic knob*. These knobs contain numerous small vesicular structures, the *synaptic vesicles* that are believed to be packages of the specific chemical substances concerned in synaptic transmission. Some of these vesicles are concentrated in zones on the membrane that fronts the *synaptic cleft*, which is the remarkably uniform space about 200 Å across, that is indicated by arrows in Fig. 1B. The chemical transmitter substance is released from the synaptic knob into the cleft and acts on the *subsynaptic membrane*. Since synaptic transmission has to occur across the synaptic cleft that is interposed between the presynaptic and postsynaptic components of the synapse, it might appear that the synaptic cleft is merely a barrier to transmission; but we shall see later that it must not be too narrow else it will unduly impede the flow of the postsynaptic electric currents that provide the essential expression of synaptic actions of all kinds. In its dimensional design the synaptic cleft approaches to optimal efficiency.

The experimental investigation of synaptic transmission was transformed[6,7]

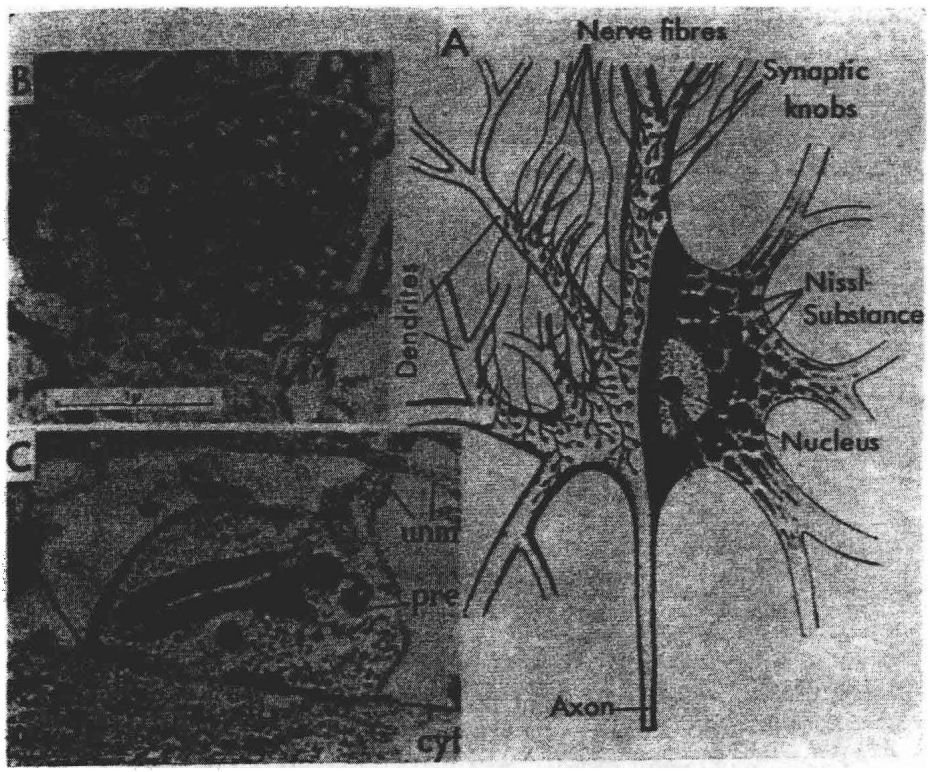

Fig. 1. (A) Diagrammatic drawing of a neurone showing dendrites and axon radiating from the cell body or soma that contains the nucleus. Several fine nerve fibres are shown branching profusely and ending in synaptic knobs on the body and dendrites (Jung[34]). (B) Electronmicrograph of a synaptic knob separated from subsynaptic membrane of a nerve cell by a synaptic cleft (marked by arrows) about 200 Å wide. In some areas the vesicles are seen to be concentrated close to the synaptic surface of the knob, and there is an associated increase in membrane density on either side of the cleft (Palay[36]). (C) Electron micrograph of an inhibitory synapse that is formed by a synaptic knob (pre) of a basket cell on the soma (cyt) of a hippocampal pyramidal cell. (Hamlyn[26])

in 1951 by the introduction of the technique of recording electrically from the interior of nerve cells. It is possible to insert into nerve cells a fine glass pipette having a tip diameter of about 0.5 μ and filled with a conducting salt solution such as concentrated potassium chloride. If this is done with rigid precautions of mechanical fixation, the cell membrane is believed to seal around the glass microelectrode, so preventing the flow of a short-circuiting current from the outside to the inside of the cell. Many impaled nerve cells appear to behave normally even for hours. In the central nervous system one is of course searching blindly for cells, but, by utilizing clues provided by the electric field po-

tentials radiating from activated cells, a great many cells can be located and successfully impaled in a single experiment. In Fig. 2 a microelectrode has been drawn on a microphotograph of one of the large nerve cells or *motoneurones* that innervates muscle, but for illustrative purposes it is magnified about five times relative to the motoneurone. It was a fortunate choice that our first in-

Fig. 2. Microphotograph of a motoneurone with radiating dendrites and axon as in Fig. 1A but superimposed on it is a drawing of the actual shape of a microelectrode shown as it would be located for intracellular recording, though with a size exaggerated about 5 times relative to the scale of the motoneurone. (Brock, Coombs and Eccles[7])

vestigations were on motoneurones, because intracellular investigations have proved to be much easier and more rewarding in these cells than on any other kind of mammalian nerve cell.

I must now digress briefly in order to give an account of the ionic composition of nerve cells and of the electrical charges on their surfaces, because both these features are essentially concerned in synaptic action. As shown in Fig. 3 A, the surface membrane of a nerve cell separates two aqueous solutions that have very different ionic composition. The external concentrations would be virtually the same as for a protein-free filtrate of blood plasma. The internal concentrations are approximate, being derived more indirectly from investigations on the equilibrium potentials for some physiological processes that are specifically produced by one or two ion species, and also from more general considerations. Within the cell, sodium and chloride ions are at a lower concentration than outside, whereas with potassium there is an even greater disparity – almost 30-fold – in the reverse direction. The *equilibrium potentials* for each species of ion are the membrane potentials at which there is equality of diffusion inwards and outwards. Under resting conditions potassium and chloride ions move through the membrane much more readily than sodium. The formal electrical diagram of Fig. 3 B gives under resting conditions the electrical properties of the surface membrane of a motoneurone as «seen» by a microelectrode inserted intracellularly as in Fig. 2. A battery of about – 70 mV (inside negativity) with an in-series resistor is in parallel with a capacitance[8,10,12,18]. Fig. 3 C shows diagrammatically the way in which a metabolically driven pump can compensate for the unbalance in diffusion of sodium and potassium ions across the surface membrane. With nerve cells the situation is believed to be very similar to that so rigorously investigated with giant axons, peripheral nerve fibres and muscle fibres by Hodgkin, Huxley and their colleagues[27-32].

The simplest example of synaptic action is illustrated in Fig. 4, where a single synchronous synaptic bombardment diminishes the electric charge on the cell membrane. A rapid rise to the summit is followed by a slower, approximately exponential, decay. This depolarization becomes progressively larger in A to C as the number of activated synapses increases, there being in fact a simple summation of the depolarizations produced by each individual synapse. In the much faster records of D to G it is seen that, when above a critical size, the synaptic depolarization evokes at the double arrows the discharge of an impulse, just as occurs in peripheral nerve. The only effect of strengthening the synaptic stimulus in E to G was the earlier generation of the