

OTTO LOEWI

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■ SCIENTIFIC
CONTEXT

■ MAIN WORK



The end of the 19th century was the starting point of many discoveries in the field of the neurophysiology.

At that time, only basic technical approaches were available, and new discoveries depended on few results and lots of deductions. Furthermore, the scientific community was often debating on theoretical speculations and was often divided.

I have chosen to present a German neurophysiologist, Otto Loewi, as he witnessed lots of debates of the late 19th century, and since he had solved the major question of synaptic transmission with quite simple experiments.

BIOGRAPHY

- 1873 3rd June, birth of Otto Loewi, in Frankfurt-am-Main (Germany). His father is Jacob Loewi, a merchant, and his mother is Anna Willstätter.
- 1891 He starts medical studies at the universities of Munich and Strasbourg (at that time part of Germany).
- 1893 He just manage to pass his first examination although he was more interested in the philosophy lectures.
- 1896 He finally brilliantly obtains his doctor's degree with a thesis about "techniques of isolations of frog's heart".
- 1898 He becomes an assistant of Pr Hans Horst Meyer, a pharmacologist.
- 1902 In London, in Starling's laboratory, he meets for the first time Henri Hallet Dale, who was to become a lifelong friend.
- 1904 He starts teaching at the University of Vienna, as a Professor in Pharmacology.
- 1909 He is appointed to the Chair of Pharmacology in Graz.



- 1921 He proves, the chemical transmission of the nerve impulses.
- 1936 He receives the Nobel price, with Henri Dale.
- 1938 He is forced to leave Austria, invaded by the Germans and moves to London.
- 1940 He travels from England to America, where he is invited to join the College of Medicine of New-York, as a Research Professor in Pharmacology.
- 1946 He becomes an American citizen.
- 1961 25th December, death.

35 years before Otto Loewi 's birth, Gabriel Gustav Valentin was the first to describe the nucleus and nucleolus of cells present in the brain.

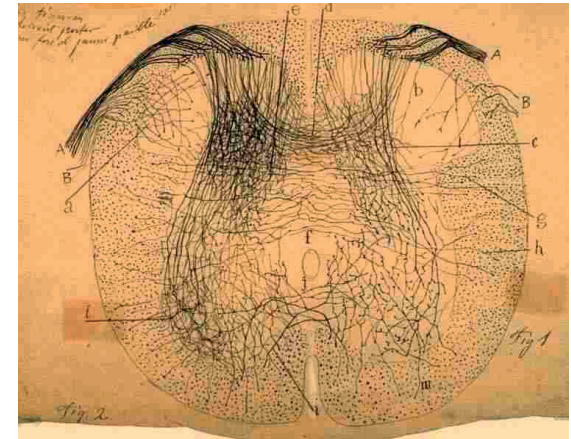
The name « neuron » was used for the first time in 1891, when Otto Loewi enters the university. He was 33 years old when Santiago Ramon Y Cajal and Camillo Golgi shared the 1906 Nobel Price for their contribution in neurophysiology, although having a completely different point of view about brain organisation. Actually, the scientific community was at that time divided about the brain organisation between reticularist and neuronal theory.

The reticularist doctrine was supported by C.Golgi :

« There is certainly to be found a very widespread network of filaments anastomosing one with the other throughout the gray matter of the brain. »

The neuronal theory had four tenets:

- The neuron is the structural and functional unit of the nervous system;
- Neurons are individual cells, which are not continuous to other neurons, neither anatomically nor genetically;
- The neuron has three parts: dendrites, soma (cell body) and axon. The axon has several terminal arborizations, which make close contacts to dendrites or the soma of other neurons;
- Conduction takes place in the direction from dendrites to soma, to the end arborizations of the axon



This theory was supported by S.R. y Cajal, R. A. von Kölliker, W. von Waldeyer and of course was the good one.

Having established that neurons do not fuse together at any level of their ramifications, a question became important. How is the contact between neurons? How the transmission of an electrical impulse wave occurs between two neurons? This «neuronal junction», was too small to be observed by the microscopes of that time.

SCIENTIFIC CONTEXT

The problem of the nature of transmission from one neuron to another was also a point of major consideration and inquiry among neurophysiologists at the turn of the 20th century. Back to 1846, Emil DuBois-Reymond proposed the existence of synapses that could be either electrical or chemical. He had no support for this speculation, and this idea was abandoned.

Many neurophysiologists defended the idea that the transmission should be electrical, just like the propagation wave along the axon. It was actually making sense to imagine electrical synapses. Unfortunately there were three important arguments against such simple picture of the nervous system.

- The first is the unidirectional flow of information in a neural chain: this flow is always in the axo-dendritic or axo-somatic way, and must be mediated by the synapse.
- The second is that scientists were accumulating evidence that there were excitatory as well as inhibitory synapses. Since it was already known that the action potential has always the same polarity, it would have been difficult to imagine a

purely electrical synapse conveying excitation or inhibition.

- The third was based on the observed delay in the transmission of impulses through a simple proprioceptive reflex. An electrical transmission should have no delay.

Many of the experiments supporting these data were carried out in the laboratory of the great British physiologist Sir Charles S. Sherrington (1852-1952), who investigated in the late 1890s the physiology of simple and complex motor reflexes.



Sherrington gave the name, «synapse», which, in Greek, means «to clasp» and he was one of the first to discover that the interplay of central excitation and inhibition are fundamental for information integration.

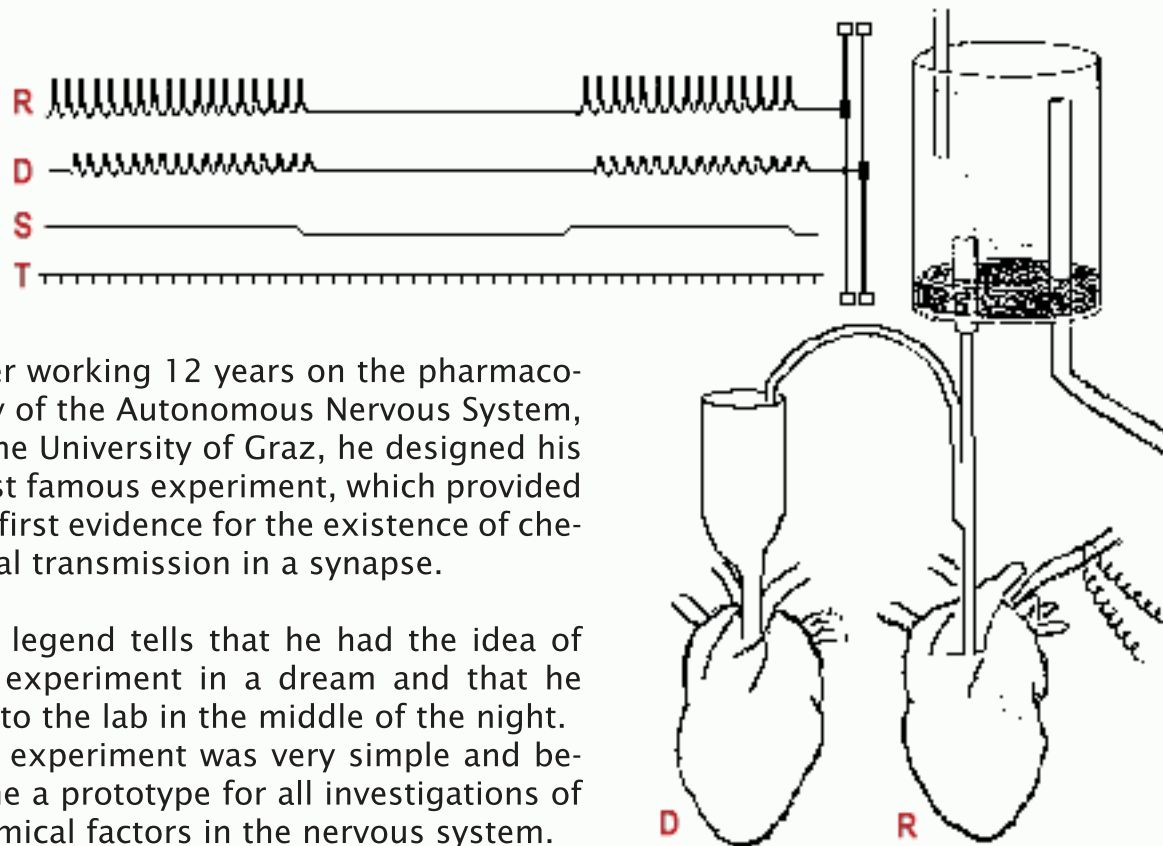
The same concepts of excitation and inhibition appeared again in the study of the peripheral nervous system, particularly in the Autonomous Nervous System (ANS).

For example, the force of contraction and heart rate increase when the so-called sympathetic division is activated (by electrically stimulating the ganglionic nerves which innervate the heart, for example). In contrast, they are decreased when the vagus nerve, which conducts the so-called parasympathetic division, is activated.

How electrical transmission in the same postsynaptic element could achieve totally opposite effects. The answer, of course, was again a chemical transmission.

All these evidences have convinced neuroscientists in the beginning of the 20th century that most synapses had chemical transmission. However the fundamental proof came only in 1921, as we will see, with the crucial experiments carried out by Otto Loewi.

MAIN WORK



After working 12 years on the pharmacology of the Autonomous Nervous System, in the University of Graz, he designed his most famous experiment, which provided the first evidence for the existence of chemical transmission in a synapse.

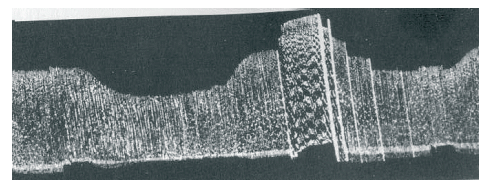
The legend tells that he had the idea of the experiment in a dream and that he ran to the lab in the middle of the night. The experiment was very simple and became a prototype for all investigations of chemical factors in the nervous system.

He cut out two hearts from frogs and perfused them with a warm physiological solution (Ringer). In this condition, the frog's hearts continue to beat for some hours. He then stimulated the vagus nerve to one of the hearts.

As a consequence, there was a strong inhibition in this heart beats (R). The second heart was unaffected.

However, when he perfused the second heart with the outflow of the perfusion of the first one, he achieved exactly the same effect (D), with a small delay provoked by the pump action and the chemical action.

It was therefore concluded that some substance produced at the parasympathetic synapse level in heart R, was able to induce a similar response in the muscles of heart D. Loewi believed that it was acetylcholine, and it was actually demonstrated later.



Loewi's original kymographic record of the experiment.

After using the same preparation to study the effects of stimulating the sympathetic nerves, he obtained an opposite effect: heart D accelerated its pace, as observed following adrenaline injection.

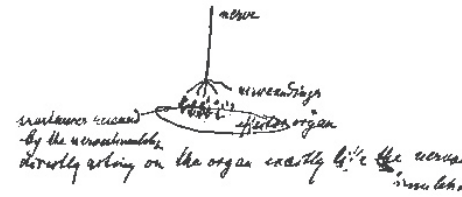
CONCLUSION & REFERENCES

Loewi doubted that such neurotransmitters also operated in the somatic nervous system.

Research in this area was much more difficult to carry out, but Sir Henry Dale again came to rescue, by proving, in a series of elegant experiments between 1929 and 1936, that acetylcholine was also a neurotransmitter in the neuromotor synapse, and that preganglionic synapses in the ANS are all cholinergic, in contrast to the postganglionic ones, which can be either cholinergic or adrenergic, as Loewi had demonstrated.

Dale also was the first to isolate acetylcholine from mammalian organs, and to propose the terms «cholinergic» and «adrenergic» synapses.

Loewi and Dale, who were friends since 1906, continued their efforts on clarifying the role of neurotransmitters. They shared the Nobel Prize of 1936 for their discoveries.



If a nerve by a stimulus gets an impulse this impulse is propagated within the nerve and is transmitted to the respective effector organ (heart, muscle, gland) innervated by the nerve. The question arose by which means the impulse coming from the nerve is transmitted to the effector organ. I was able to solve this question by proving that the impulse running down within the nerve liberates from its endings chemical substances (acetylcholine or adrenaline respectively) which in their turn influence the effector organ exactly like the stimulation of the nerve. With other words: the effect of nervous stimulation on the organ is not a direct one but an indirect one mediated to the organ by the chemical substances released by the nerve terminals in its endings.

Otto Loewi

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