Clin. Cardiol. 29, 135–136 (2006)

Profiles in Cardiology

This section edited by J. Willis Hurst, M.D., and W. Bruce Fye, M.D., M.A.

Otto Loewi and the Chemical Transmission of Vagus Stimulation in the Heart

HEINZ-GERD ZIMMER, M.D.

Carl-Ludwig-Institute of Physiology, University of Leipzig, Leipzig, Germany

Otto Loewi (1873–1961) (Fig. 1) was born in Frankfurt/Main, Germany. After attending school in his native town he started to study medicine at the University of Munich in 1891 and completed his studies at the University of Strasbourg in 1896. He then took a course in inorganic chemistry in Frankfurt and spent a few months in the biochemical institute of Franz Hofmeister in Strasbourg. During 1897 and 1898, he worked at the City Hospital in Frankfurt. He became frustrated by the lack of therapy in the treatment of tuberculosis and pneumonia and decided to do research in basic medical science, in particular, in pharmacology.

Otto Loewi succeeded in becoming assistant to Hans Horst Meyer at the University of Marburg and was appointed lecturer in 1900. In 1902, he spent some months in the laboratory of Henry Starling where he met W. M. Bayliss and Henry H. Dale. In 1909, he was appointed professor of pharmacology and chairman at the University of Graz, Austria. In 1936, together with Sir Henry Hallett Dale (1875–1968), he was awarded the Nobel Prize in Physiology or Medicine for their discoveries relating to chemical transmission of nerve impulses. When Austria was annexed by the Nazis in 1938, Loewi was forced to leave the country. He had been compelled to instruct the Swedish bank in Stockholm to transfer his Nobel Prize money to a Nazi-controlled bank. He fled first to Brussels, Belgium, where he spent some time as Visiting Professor at the Université Libre, and then to Oxford, Great Britain, where he was at the Nuffield Institute. In 1940, he moved to the U.S. and worked at the College of Medicine, New York, as Research Professor of Pharmacology. In 1946, he became an American citizen. He died in 1961.[1]

The work that led to the Nobel Prize was primarily concerned with the effects of vagus stimulation on heart function. In 1845, Eduard Weber (1806–1871) and his elder brother Ernst Heinrich Weber (1795–1878) had shown an interest in this issue. They demonstrated that electrical stimulation of parts of the brain in which the vagus originates, as well as stimulation of the vagus nerve itself, reproducibly slowed and eventually stopped the heart beat.[2] At that time, however, the kymograph that Carl Ludwig introduced into physiologic research[3] was not available, so that registration and documentation of the effect were not possible. The effects were therefore demonstrated by E. H. Weber during the meeting of the Italian natural scientists in Naples in 1845.

The negative chronotropic and inotropic effects of vagus stimulation were also observed by Albert von Bezold[4] and documented in the frog heart in Carl Ludwig's (1816–1895) Leipzig Physiological Institute by Joseph Coats, a Scotsman from Glasgow. A frog was cut below the liver, and the sternum and front feet were excised, but a large skin patch was maintained to serve as a cover for the nerves and heart. The aorta was cannulated and connected with a mercury manometer. Another cannula was inserted into the atrium and connected to the reservoir, which contained reddish rabbit serum.[5] The vagus nerve was stimulated with platin electrodes. This preparation was a nonrecirculating system in which the heart pumped the serum into the manometer and caused regular and consistent excursions of the mercury, which reflected the force developed by the heart. As soon as vagus nerve stimulation became effective, there was an immediate decrease in systolic and diastolic pressure, and beating stopped entirely. When the heart resumed its action, the rate was slower and the amplitude of contractions was lower. Both increased until the normal contraction pattern was attained.[6] In this frog heart preparation, Schmiedeberg tested the effect of atropine, muscarine, and nicotine. He demonstrated that the negative

Address for reprints:

Heinz-Gerd Zimmer, M.D.
Professor of Physiology, Chair
Carl-Ludwig-Institute of Physiology
University of Leipzig
Liebigstrasse 27
D-04103 Leipzig, Germany
e-mail: zimmer@medizin.uni-leipzig.de

Received: September 13, 2004
Accepted: September 13, 2004

FIG. 1 Otto Loewi (1873–1961). Reprinted from Ref. No. 9 with permission of the publisher.

chronotropic effect of vagus stimulation was prevented by nicotine and noted that atropine can be used to eliminate the effects of the "inhibitory apparatus" of the heart.[7]

For his experiments, Otto Loewi used the isolated heart of the frog and the toad.[8] The heart was perfused via a Straub cannula, and the left vagus nerve was preserved. He filled hearts with Ringer solution with and without electrical stimulation of the vagus. Vagus stimulation had the well known negative inotropic and chronotropic effect. "Then the Ringer solution that had been in the first heart during the stimulation of the vagus was transferred to the second heart. It slowed and its beats diminished just as if its vagus had been stimulated."[9] This effect was antagonized by atropine (Fig. 2). In the toad, stimulation of the vagus had a positive inotropic effect. This could also be induced by using the perfusion fluid obtained during nerve stimulation. Otto Loewi concluded that a heart-inhibiting ("Vagusstoff") or stimulating substance must have been released into the perfusion fluid during vagus stimulation. He excluded potassium as the transmitter, since the potassium effect could not be antagonized by atropine.[8]

In a series of successive papers, Loewi characterized the substance released by vagus stimulation in more detail. He showed that the transmitter appeared subsequent to nerve stimulation and was not a product of the arrest of the heart, since he did not detect the vagus substance when he induced cardiac arrest by applying the first Stannius ligature. He also

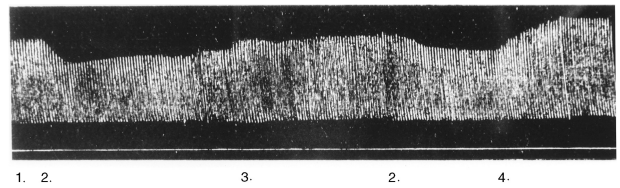

FIG. 2 The effect of the vagus substance (Vagusstoff) on the contraction of the isolated frog heart. 1. Perfusion with Ringer solution. 2. Perfusion with Ringer solution obtained during a 15-min period of vagus stimulation. 3. Perfusion with Ringer solution obtained during a 15-min control period. 4. Addition of 0.1 mg atropine. Original Figure 1 from Ref. No. 8.

excluded choline as the responsible transmitter.[10] Finally, Loewi showed that the vagus substance loses its effect when it is in contact with a native aqueous heart extract—with cholinesterase, for example—to the same extent as does acetylcholine.[11] Taken together these results were convincing and were generally accepted as evidence that acetylcholine is the chemical transmitter of the vagus in the heart.[12] This organ was the first in which chemical transmission was demonstrated.

References

1. Otto Loewi—Biography. http://www.nobel.se/medicine/laureates/1936/loewi-bio.html
2. Weber EH: Ueber Eduard Weber's Entdeckungen in der Lehre von der Muskelcontraction. *Arch Anat Physiol* 1846;483–527
3. Ludwig C: Beiträge zur Kenntnis des Einflusses der Respirationsbewegungen auf den Blutlauf im Aortensysteme. *Arch Anat Physiol wiss Med* 1847; 242–302
4. von Bezold A: Zur Physiologie der Herzbewegungen. *Virchows Arch* 1858;14:282–309
5. Zimmer H-G: Modifications of the isolated frog heart preparations in Carl Ludwig's Leipzig Physiological Institute: Relevance for cardiovascular research. *Can J Physiol* 2000;16:61–69
6. Coats J: Wie ändern sich durch die Erregung des n.vagus die Arbeit und die innern Reize des Herzens? Berichte über die Verhandlungen der Königlich Sächsischen Gesellschaft zu Leipzig. Mathematisch-Physische Classe 1869;21:360–391
7. Schmiedeberg O: Untersuchungen über einige Giftwirkungen am Froschherzen. Berichte über die Verhandlungen der Königlich Sächsischen Gesellschaft zu Leipzig. Mathematisch-Physische Classe 1870;22:130–141
8. Loewi O: Über humorale Übertragbarkeit der Herznervenwirkung. I.Mitteilung. *Pflügers Arch Ges Physiol* 1921;189:239–242
9. Heymans CJF, Folkow B: Vasomotor control and the regulation of blood pressure (Eds. Fishman AP, Richards DW), pp. 407–486. In *Circulation of the Blood. Men and Ideas*. American Physiological Society, Bethesda, Maryland 1982
10. Loewi O: Über humorale Übertragbarkeit der Herznervenwirkung. II.Mitteilung. *Pflügers Arch Ges Physiol* 1921;193:201–213
11. Loewi O, Navratil E: Über humorale Übertragbarkeit der Herznervenwirkung. X.Mitteilung. Über das Schicksal des Vagusstoffes. *Pflügers Arch Ges Physiol* 1926;214:678–688
12. Sir Henry Dale—Nobel Lecture. http://www.nobel.se/medicine/laureates/1936/dale-lecture.html.