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THE CHEMICAL LANGUAGES OF THE NERVOUS SYSTEM

HISTORY OF SCIENTISTS AND SUBSTANCES

6 figures, 1 in color, 2006
In grateful memory to my teacher in pharmacology
Sir John Henry Gaddum

F.L.
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PREFACE

Documentation Otto Loewi

The collection of documents of Otto Loewi and his family consisted in 1962 primarily of a large suitcase full of unselected material that was in the hands of his son Guido. It was filed carefully by Wolfgang Giere and supplemented with material of various sources between 1962 and 1965. The collection of 13 bureau files was handed over by Guido Loewi to the Royal Society on November 17, 1965, and is stored there under the name ‘Documentation Otto Loewi’. It served as the basis for the book by Lembeck and Giere [1968]: Otto Loewi: Ein Lebensbild in Dokumenten.

During the following 30 years, additional material came into my hands. Other documents resulted from a search of Anton Kernbauer in archives and elsewhere. The resulting Supplement 1999, collected in 3 bureau files, was added to the existing collection at the Royal Society on June 5, 2000.

Not included in the Supplement 1999 are the transcripts of interviews of Ulrich and Anna Weiss in November 1990, done as part of the ICCGW’s Holocaust Oral History Project, amounting to 130 typed pages.

The continuing support by Anna Weiss-Loewi and Guido Loewi has to be mentioned in particular. Numerous talks with Anna Weiss-Loewi and her husband Ulrich, and with Guido provided the information condensed in the chapter ‘The Loewi Family’s Way to the New World’ (see pp. 11–29). Generally, I think it can be said that the life of Otto Loewi is better documented than that of any other prominent scientist.

Insert

When the recollections of only one contributor have been recorded, his initials are inserted in parentheses at the end of the sentence (e.g. F.L. = Fred Lembeck or J.D. = Josef Donnerer). As the older contributor, I (F.L.) would like to thank my friend and co-author J.D. We would both like to express our gratitude to the head of our department Prof. Dr. Bernhard A. Peskar for his continuous support.

Reference

The first localization of a receptor was achieved by Claude Bernard [1878] when he demonstrated by simple experiments that curare acts on the motor end plate without influencing nerve fibres or the central nervous system.

The English physiologist John Newport Langley (1852–1926) arrived at the concept of receptor sites for drug action from a study of pilocarpine and atropine on salivary secretion, which led him to conclude in 1878 that ‘there is some “receptor” substance with which both atropine and pilocarpine are forming compounds according to some law in which their relative mass and chemical affinity for the substance are factors’. Langley [1905] concluded that ‘there is a chemical combination between the drug and a constituent of the cell – the receptive substance’.

The German physician, biologist and chemist Paul Ehrlich was responsible for a more general concept of receptors, based on his work with tissue stains, immunity and chemotherapy. Ehrlich postulated (1885) that the specific activities of cellular protoplasm could be moderated by ‘side chains’ or ‘receptors’, to which a haptophoric group of drugs or toxins was attached and if the drug or toxin also contained a toxophoric group, the cell was damaged or killed. Ehrlich’s emphasis on the binding of drugs to protoplasmic side chains (receptors) was summed up (1913): ‘If the law is true in chemistry that corpora non agunt nisi liquida [drugs will not work unless they dissolved], then for chemotherapy the principle is true that corpora non agunt nisi fixata [drugs will not work unless they are bound]’ [see Bowman and Rand, 1980; Rang et al., 2003].

Alfred Joseph Clark (1926) quantified the relationships of dose and its effect of agonists alone and also under the influence of an antagonist. He used acetylcholine as an agonist and atropine as its antagonist on a simple preparation, a strip of the frog’s heart. The ventricle strip was stimulated electrically at 3-second intervals to contract, the contraction being reduced by acetylcholine. By ingenious calculations he determined the quantity of the agonist action upon each cell. The amount of drug that is fixed by the cell is very small: only 20,000 molecules fixed per cell are sufficient to produce a demonstrable action; this number of molecules could occupy only a very small fraction of its surface. He concluded that a reversible monomolecular reaction occurs between the drug and some substance either in the cell or on its surface [see Clark, 1985].

In 1887 the young Spanish Professor Santiago Ramón y Cajal proposed the structure of the brain with not much more than a simple light microscope, pen and paper, specimens of brain tissue and the tissue-staining method of the Italian histologist Camillo Golgi. Cajal suggested that the neurons receive information at their dendrites and cell bodies and relay nerve impulses through their axons. He stated that the axons ended and formed contacts (later termed synapses by Charles Sherrington) to dendrites and other nerve cell bodies. The unseen synaptic gaps were the basis of neurotransmission. In contrast to the ‘reticular theory’ of Golgi, Cajal tactfully defended his ‘neuron doctrine’ at their first meeting, when both received the Nobel Prize in Physiology or Medicine in 1906 [for a review, see Rapport, 2005].
One neuron sends information to another at the point of contact known as synapse. The main debate related to synaptic transmission was whether it was chemical by the release of neurotransmitters, or electrical like the nerve impulse itself. Physiologists believed that fast synaptic transmission had to be electrical. They used modern methodology and tools such as the cathoderay oscilloscope, whereas pharmacologists were still using bioassays and old-fashioned recording methods. But new technology finally convinced the physiologists that synapses do communicate by the release of neurotransmitters. John Eccles, one of the strongest proponents of electrical transmission in synapses, finally provided some of the key evidence that he, and the other physiologists, had been wrong. Eccles was a friend and great admirer of Dale [for a review, see Valenstein 2005].

A picturesque situation concerning the receptor concept has been described by de Jongh [1964]:

‘To most modern pharmacologists the receptor is like a beautiful but remote lady. He has written her many a letter and quite often she has answered the letters. From these answers the pharmacologist has built himself an image of this fair lady. He cannot, however, truly claim ever to have seen her, although one day he may do so... and the beautiful lady soon appeared.’

In the 1970s, pharmacology entered a new phase. Receptors emerged as biochemical realities. The availability of tightly bound radioactive ligands made it possible to extract and purify the radioactively labelled receptor material [see Burgen, 1970]. This approach was first used successfully on the nicotinic acetylcholine receptor. Meanwhile, the molecular aspects of receptor-mediated mechanisms have advanced so far that they are dealt with in separate chapters in a modern textbook of pharmacology.

Transmitter substances and other types of mediator are the ‘keys’ by which the receptor is ‘turned’ into an active shape, to form the sensing element in the system of chemical communication that coordinates the function of cells.

Agonists and antagonists of transmitter substances, including their synthetic analogues, provided the pharmacological basis for their therapeutic application.

The chemical transmission of nervous impulses was the key to many discoveries in pharmacology and other fields of life sciences and medicine. This is specifically true for the discovery of receptors, and agonists and antagonists acting on them. The historical experiments resulted in facts, now to be found in textbooks. The neurochemical transmission, initially demonstrated at the peripheral terminals of efferent autonomic nerve fibres, has been found in all types of efferent and afferent peripheral nerve fibres, in the enteric nervous system and in the countless nerve connections of the central nervous system. The chemical neurotransmission can be regarded as the overall used chemical language, in which nerves talk to each other or to organs.

The initial findings centred around the experimental work of Henry H. Dale, Otto Loewi and W. Feldberg. Their historical findings opened the door to further investigations of neurotransmitters and extended the list of neurotransmitters to include further monoamines, amino acids, peptides, purines and nitric oxide.

The aim of this publication is to provide information about the scientists involved in the early discoveries, their experiments and their substances. Their documented memoirs, obituaries and photos, only supplemented by comments, should provide the reader with basic information about their personality, their scientific approach and their life at times which were anything but quiet and peaceful. The texts written by the scientists should also demonstrate to the reader how unexpected findings were sometimes the basis of a discovery.

Not only scientists have their history, but also the substances used by them, such as transmitters, their antagonists and other tools to influence their action. Modern textbooks of phar-
macology primarily provide facts about drugs which are important for therapeutic use. The stories about these substances, from their discovery on, might also interest readers. They are, therefore, included in the second part of this book, containing some anecdotes and unusual events on the way to their therapeutic application.

References
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