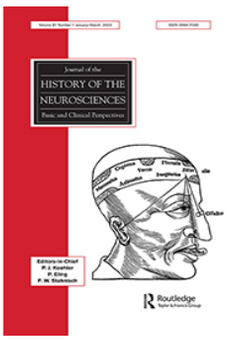

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The neurosciences at the Max Planck Institute for Biophysical Chemistry in Göttingen

Heinz Wässle[a] and Sascha Topp[b]

[a]Max Planck Institute for Brain Research, Frankfurt/Main, Germany; [b]Max Planck Institute of the History of Science, Berlin, Germany

ABSTRACT

The Max Planck Institute (MPI) for Biophysical Chemistry (Karl-Friedrich Bonhoeffer Institute) was founded in 1971 in Göttingen. Two of the 11 departments at the institute had a neuroscientific focus. Otto D. Creutzfeldt (1927–1992) and Victor P. Whittaker (1919–2016) were directors of the Neurobiological and Neurochemical Departments, respectively. Creutzfeldt's department researched the structure and function of the cerebral cortex, and Whittaker's department concentrated on the biochemical analysis of synapses and synaptic vesicles. Creutzfeldt and Whittaker were already internationally respected scientists when they were appointed to Göttingen. The next generation of departmental directors, Erwin Neher and Bert Sakmann, were "home-grown" researchers from the institute and, during their time as junior group leaders, they developed the so-called patch clamp technique, with which they were able to measure single ion channels in nerve cells. This technique revolutionized neurophysiology, and Neher and Sakmann were awarded the 1991 Nobel Prize in Physiology or Medicine for their work in this area. Neher was appointed director of the Membrane Biophysics Department in 1983 and, since then, his department has mainly examined the role of Ca^{2+} in the release of neurotransmitters at synapses and in the secretion of catecholamines from chromaffin cells. From 1985, Sakmann was director of the Cell Physiology Department, and his laboratory concentrated on the molecular and physiological characterization of transmitter receptors in postsynaptic membranes. In 1989, he was appointed to the MPI for Medical Research in Heidelberg. Reinhard Jahn became director of the Neurobiology Department in 1997, researching the molecular mechanisms of the release of neurotransmitters from the presynaptic terminals, and he discovered several proteins associated with the synaptic vesicles. With their work, Neher, Sakmann, and Jahn have made the MPI for Biophysical Chemistry one of the world's leading research centers for the transmission of signals at synapses.

KEYWORDS

Cerebral cortex; Göttingen neuroscience; patch clamp recording; release of neurotransmitters; synaptic vesicles; vesicle associated proteins

Introduction

The Max Planck Institute (MPI) for Biophysical Chemistry (Karl Friedrich Bonhoeffer Institute) was established on the initiative of the Nobel laureate

CONTACT Heinz Wässle heinz.waessle@brain.mpg.de Max Planck Institute for Brain Research, Max von Laue Strasse 4, D–60438 Frankfurt/Main, Germany.

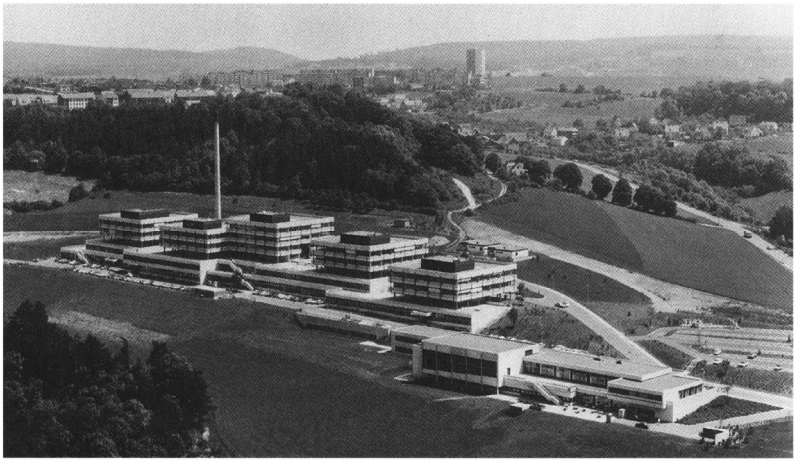

Figure 1. The Max Planck Institute for Biophysical Chemistry was built from 1968 to 1972 roughly six kilometers outside of Göttingen on the crest of a gently sloping hill called Fassberg, by the architect Walter Henn (1912–2006). In the middle of the photo, one can see the five "towers," which are actually laboratory buildings. The town of Nikolausberg is in the background (taken from Uebele, 1998). Source: Figure 68 in Uebele, S. 1998. *Institute im Bild Teil II: Bauten der Max-Planck-Gesellschaft zur Förderung der Wissenschaften*. Berlin: Eckart Henning. Archive on the History of the Max Planck Society, Volume 11.

Manfred Eigen (1928–2019)[1] and officially opened in 1971 (Figure 1). The institute resulted from merging the MPI for Physical Chemistry with the MPI for Spectroscopy (Balcar 2020, 123–124).[2] In turn, the MPI for Physical Chemistry—founded by the Max Planck Society in Göttingen in 1949, with Karl Friedrich Bonhoeffer (1899–1957) as its first director—was, together with the later Fritz Haber Institute, one of the two successor institutes of the former Kaiser Wilhelm Institute (KWI) for Physical Chemistry and Electrochemistry (Berlin; see Henning and Kazemi 2016, 290–300; James et al. 2011, 148–153).[3]

Bonhoeffer was a physical chemist, and he brought an interdisciplinary alignment to the institute, working on biological questions alongside electrochemistry and membrane research. Bonhoeffer had already begun his work on the Ostwald Lillie model of nerve conduction during his time as professor of physical chemistry in Leipzig (1934–1947). The Ostwald Lillie model in a way represents the behavior of a nerve fiber: An iron wire placed in concentrated nitric acid, when depolarized, shows a wave of activity that moves along the wire at a constant speed. Just as with a nerve axon, there is an excitation threshold; a reftractory time; and, in cases of strong excitation, periodic discharges (Schindewolf 2002). It was not until after World War II that Karl Friedrich Bonhoeffer and his colleagues at the MPI for

[1]Manfred Eigen presented the concept for the new institute at the meeting of the Chemical Physical Technical Section (CPTS) of the Max Planck Society on June 9, 1964; at the December 3, 1964, meeting, the CPTS decided to set up the institute. See the minutes of the CPTS meeting from June 9, 1964, in Hamburg, AMPG, II. Abt., Rep. 62, Nr. 1743, and from December 3, 1964, in Düsseldorf, AMPG, II. Abt., Rep. 62, Nr. 1744. See also the minutes of the meeting of the Biological Medical Section (BMS) of the Max Planck Society from June 10, 1970, AMPG, II. Abt., Rep. 62, Nr. 1597.
[2]Minutes of the 67th session of the Senate from November 24, 1970 in Stuttgart, AMPG, II. Abt., Rep. 60, Nr. 67.
[3]Minutes of the fourth session of the Senate from March 18/19, 1949 in Göttingen, AMPG, II. Abt., Rep. 60, Nr. 4.

Physical Chemistry were able to take up again and expand this research into models of the saltatory conduction in nerves (Franck 1952, 1951). In a review article, Bonhoeffer summarized the nerve excitation model as follows:

> If one looks at the entire field of physiological properties and activations of a nerve, at first glance it seems astounding how many of them one can reproduce using inanimate models. This is only possible because the material, which appears to be so unbelievably diverse, can basically be reduced to only a few things. One often tends to see something specifically living in the activity of nerves that would appear to mock a physical–chemical analysis. There is no doubt about the fact that we are far removed from a full understanding. However, the puzzles are not to be found where the layman might initially suppose. We also find stimulus thresholds, saltatatory conduction and rhythmic spontaneous activity in inanimate objects, and it is the living nerve in particular that is imitated by them. . . . However, the living nerve renews itself again and again. Its energy is supplied continuously by the metabolism, in particular by the breath. The process by which all of this happens still remains pretty much in the dark to the present day. (Bonhoeffer 1953, 311)

Bonhoeffer passed away suddenly and unexpectedly in 1957; however, his pioneering work on nerve activity was continued and expanded on at the new MPI for Biophysical Chemistry. Manfred Eigen was, beyond any doubt, the "mastermind" in setting up this new multidisciplinary institute: He had the vision to explore the physical, chemical, and biological basis of complex living systems (Pecht and Jovin 2019).

Initially, still at the Max-Planck-Institute for Physical Chemistry, Eigen developed the so-called relaxation measurement method and determined chemical reaction times at the micro- and nanosecond scale. In 1967 he received, together with Ronald George Wreyford Norrish (1897–1978) and George Porter (1920–2002), the Nobel Price for Chemistry for their studies of extremely fast chemical reactions.[4]

Later, Manfred Eigen turned his attention to the problem of self-organization of matter and the evolution of biological macromolecules (Eigen 1971). He had a strong interest in the storage and processing of information in macromolecular systems, in memory formation and ultimately in the neurosciences.

Francis O. Schmitt (1903–1995) from the MIT had organized several seminar series in the early 1960s, which brought together researchers—among them, Manfred Eigen—who were interested in bridging the gap between physical, chemical, and structural studies of the brain, on the one hand, and behavioral, psychological, and psychiatric studies, on the other hand. Participants at these meetings, including Manfred Eigen, became the founding members of the Neurosciences Research Program (NRP) and the Neuroscience Research Foundation (NRF; see Adelman 2010).

From May 4 to May 6, 1964, Manfred Eigen organized a joint meeting of the NRF and the German Society for Physical Biology in the Castle Berlepsch near Göttingen. Francis O. Schmitt summarized at this meeting the contribution of chemical-dynamical processes to the storage of information in the central nervous system (Eigen 1964). On June 9, 1964—at the meeting of the Chemistry, Physics, and Technology Section (CPTS) in Hamburg—Eigen proposed exactly this topic as part of the research program of a new institute in Göttingen.[5] The new institute was opened in 1971 and the Department for Neurobiology,

[4]See https://www.nobelprize.org/prizes/chemistry/1967/summary/ (accessed May 27, 2020).
[5]Minutes of the meeting of the Chemistry, Physics, and Technology Section of the Scientific Council on June 9, 1964, in Hamburg, AMPG, II. Abt., Rep. 62, Nr. 1743.

headed by Otto Detlev Creutzfeldt (1927–1992), and the Department for Neurochemistry, headed by Victor Percy Whittaker (1919–2016), were installed to bridge the gap between systems and molecular neurosciences.

Department for Neurobiology (1971–1992), Director: Otto D. Creutzfeldt

Otto Creutzfeldt had already been a scientific member at the MPI for Psychiatry in Munich for seven years[6] when he accepted the offer from the Max Planck Society to transfer to the MPI for Biophysical Chemistry in Göttingen.[7] Wolf Singer describes Creutzfeldt's extensive research career in Munich in an interview published in this issue.[8] All we will look at here are the 20 years Otto Creutzfeldt spent at the Göttingen Institute.

Scientific work cannot be separated from the researcher who carries it out, and this was especially true for Otto Creutzfeldt. He studied theology and philosophy before he enrolled in medicine and he wanted to understand what it meant to be human (Singer 1992). He explored the brain and the mind, and neurology, psychology, and philosophy were all part in his resarch (Figure 2).

As the cerebral cortex plays a decisive role in human behavior, thought, and self-awareness, Creutzfeldt concentrated almost exclusively on this part of the nervous system in his research work (Creutzfeldt 1983). Following his formative phase from 1953 to 1959, working under Richard Jung (1919–1986) in Freiburg, he spent most of his life studying "vision" and the visual system. Richard Jung was Germany's leading neurologist in the period after World War II and is considered the founder of clinical neurophysiology (Dichgans 2013). Jung completed his Ph.D. in 1935 in Munich under the supervision of Hugo Spatz (1888–1969), the later director of the KWI for Brain Research; from 1937 to 1938, he was a colleague of Alois E. Kornmüller (1905–1968) at the KWI for Brain Research in Berlin-Buch. Together, they carried out important work on the characterization of the electroencephalogram (EEG) in humans (Borck 2018; Jung 1992).

Creutzfeldt is regarded as one of the pioneers of research into nerve cells in the visual cortex using micro-electrodes. While still in Munich, he and his colleagues at the time, Louis A. Benevento (b. 1941) and Ulrich Kuhnt (b. 1940), succeeded in registering the responses of nerve cells in the visual cortex to moving light stimuli using intracellular recordings (Benevento, Creutzfeldt, and Kuhnt 1972; Creutzfeldt, Kuhnt, and Benevento 1974). The extensive resources available at the new institute in Göttingen allowed Creutzfeldt to broaden the focus of his department. Together with his colleagues Klaus Albus (b. 1939), Barry Lee (b. 1946), and Giorgio Innocenti (b. 1943), he studied the functional architecture of the primary visual cortex (Area 17) in cats (Creutzfeldt, Innocenti, and Brooks 1974; Lee et al. 1977). In cooperation with Tadaharu Tsumoto (b. 1942), he was able to show that inhibitory *γ-amino-*

[6]The BMS and the Senate decided on June 22 and 23, 1966, to appoint Creutzfeldt as a scientific member. See the minutes of the BMS of the Scientific Council from June 21, 1966, AMPG, II. Abt., Rep. 62, Nr. 1588, as well as the minutes of the 51st session of the Senate from June 23, 1965, in Ludwigshafen/Rh, AMPG, II. Abt., Rep. 60, Nr. 51.

[7]The Senate of the Max Planck Society had approved the appointment of Creutzfeldt to Göttingen on November 24, 1970; see the minutes of the 67th session of the Senate from November 24, 1970, in Stuttgart, AMPG, II. Abt., Rep. 60, Nr. 67.

[8]See Singer and Topp (2021).

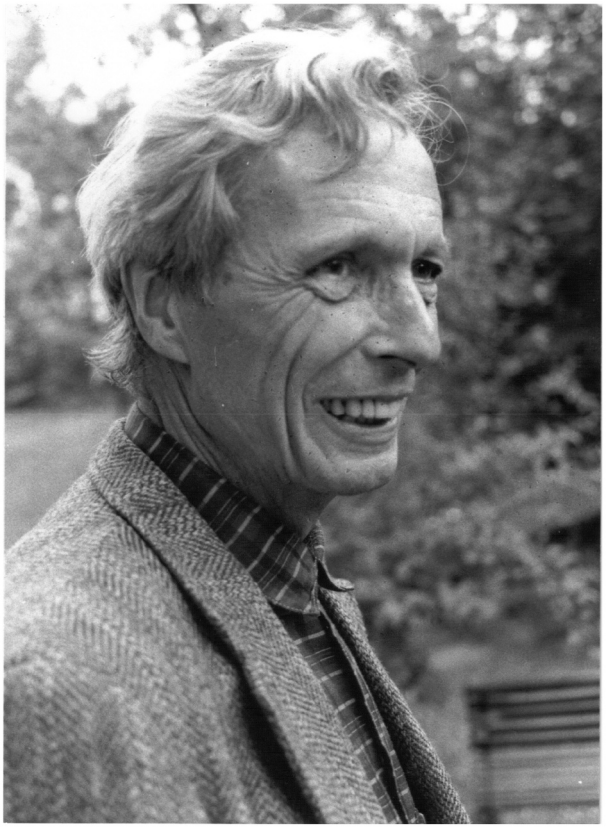

Figure 2. Otto Detlev Creutzfeldt at age 60. His father, Hans Gerhard Creutzfeldt (1885–1964), was a neurologist, psychiatrist, and neuropathologist who, together with Alfons Maria Jakob (1884–1931), discovered the Creutzfeldt–Jakob Disease (CJD), the most common form of transmissible spongiform encephalopathies caused by prions. His maternal grandfather was the well-known sociologist and economist Werner Sombart (1863–1941; taken from Albowitz et al. 1994). Source: The photo is a private gift from Mary Creutzfeldt, Otto Creutzfeldt's widow. It was also published in Albowitz, B., K. Albus, U. Kuhnt, H.-Ch. Nothdurft, und P. Wahle (eds., 1994), *Structural and Functional Organization of the Neocortex*. Proceedings of a Symposium in the Memory of Otto D. Creutzfeldt, May 1993. Berlin: Springer Verlag. Experimental Brain Research Series 24.

butyric acid (GABAergic) connections play an important role in generating the specific light responses of cells in the visual cortex (Tsumoto, Eckart, and Creutzfeldt 1979). From around 1980 onward, Creutzfeldt's research work focused on examining color perception in the visual system of primates (Creutzfeldt, Lee, and Elepfandt 1979; Kastner et al. 1992). During a nine-month sabbatical in Seattle (1984–1985), Creutzfeldt once again returned to clinical neurology. To his mind, the time had come when it was possible to translate the results from research on cats and monkeys to human beings.[9]

[9]Personal application for approval from Otto D. Creutzfeldt to Reimar Lüst, president of the Max Planck Society, 22.3.1984. Creutzfeldt's personnel file, Otto Detlev, Bd. 2.2, AMPG, II. Abt., Rep. 67, Nr. 433, Folios 621–622.

George A. Ojemann (b. 1935) was professor of neurosurgery at the University of Washington Medical School, and Creutzfeldt carried out important neurophysiological research with him on the representation of human language in the cortex. During a craniotomy in a patient who was kept awake during the neurosurgical operation, single neurons were recorded using micro-electrodes in the lateral temporal lobes of patients and their reaction while speaking and hearing was measured (Creutzfeldt, Ojemann, and Lettich 1989a, 1989b).

Besides the projects in which he himself was actively involved, Creutzfeldt always promoted younger scientists, giving them the opportunity to work on research projects independently. See Henning Scheich (b. 1942), who had been a doctorate student under Creutzfeldt in Munich, began his work on the auditory system at the Department for Neurobiology. In 1974, he was appointed professor of zoology/neurobiology at the Technical University of Darmstadt; in 1992, he became director of the Leibniz Institute for Neurobiology in Magdeburg.

Günter Rager (b. 1938) worked in the Department of Neurobiology on the embryonic development of the brain until 1980 and became director of the Institute for Anatomy and Embryology at the University of Fribourg (Switzerland) in 1980. Joachim R. Wolff (b. 1935) was head of the Working Group for Neuroanatomy until 1977, and from 1980 professor for histology and neuroanatomy at the University of Göttingen. Christoph von der Malsburg (b. 1942) set up and headed the Working Group for Theoretical Neuroscience in Creutzfeldt's department from 1973 to 1987. Subsequently, he became professor for neuroinformatics at the University of Southern California and cofounded the Institute for Neuroinformatics at Ruhr University in Bochum in 1990. Wolfgang Wuttke (b. 1942) carried out research work in Creutzfeldt's department in the area of neuroendocrinology and subsequently became director of the Department for Clinical and Experimental Endocrinology at the University of Göttingen.

Otto Creutzfeldt not only promoted the people who worked in his department, he also had a considerable impact on the neurosciences in Germany at large. He organized the Neurobiology Conference (*Neurobiologentagung*) in Göttingen every year during the Pentecost holiday. It was initially held in the lecture hall of the MPI for Biophysical Chemistry, but when this became too small, the conference moved to the University of Göttingen's auditorium building and was organized by Creutzfeldt in cooperation with the professor for zoophysiology, Norbert Elsner (1940–2011)[10] (see Heisenberg 2012). The conference became the Forum of Neuroscience in Germany, with more than a thousand, mainly young scientific researchers taking part in it every year. The conference also gave birth to the German Neuroscience Society, and it still takes place with participants coming from all over Europe. Creutzfeldt was also cofounder of the European Neuroscience Association and the *European Journal of Neuroscience*. To celebrate his 65th birthday, Creutzfeldt's former colleagues organized a scientific symposium in the fall of 1992 in his honor. Sadly, Creutzfeldt died at the beginning of 1992, and the symposium was held posthumously in his memory in May 1993 in Göttingen.

[10]See https://web.archive.org/web/20070921180811/http://www.znv.de:80/mem_elsner.shtml (accessed May 28, 2020).

His students and colleagues, as well as many leading researchers from the field of brain research, came together once again to honor Otto Creutzfeldt and to present their latest research (Albowitz et al. 1994).

Department for Neurochemistry (1973–1987), Director: Victor P. Whittaker

Synapses are the points of contact between individual neurons and mediate the signal transfer in the nervous system. The term *synapse* was introduced in 1897 by the British neurophysiologist and later Nobel laureate Charles Sherrington (1857–1952), long before its structure and function were clarified (Valenstein 2005, 4) and, above all, against the bitter resistance of the so-called "reticularists," who believed that nerve cells formed a syncytium (Nissl 1903). In the first half of the last century, first the functional roles of synapses were studied—that is, the chemical signal transmission by a neurotransmitter, its quantal release, and its effect on the postsynaptic nerve cells. When electron microscopy, which had been developed from the 1930s onward, came into use in 1954 (Hentschel 2014, 311; Ruska 1955), it became possible to examine the structure of the synapses, showing that they contained large quantities of small blisters known as vesicles and that the membranes are thickened at the contact points (Figure 3; see De Robertis 1964, 27–48; Cowan and Kandel 2001, 1–87).

From 1959, Victor Whittaker carried out important and ground-breaking work on the function of the synaptic vesicles and on the role of acetylcholine as a neurotransmitter (Zimmermann and Fonnum 2016). Two technical innovations made this success possible: the availability of adequate centrifuges and introduction of electron microscopy (Zimmermann 2018). Whittaker managed to fractionate the brain tissue of mammals and

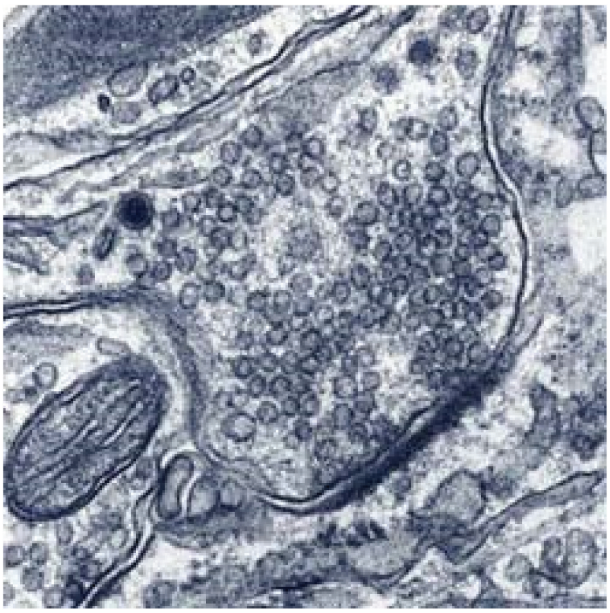

Figure 3. Electromicroscopic image of a synapse between hippocampal cells in culture. The small round bubbles are the synaptic vesicles that are filled with a neurotransmitter. Photo courtesy of Jürgen Klingauf, Max Planck Institute for Biophysical Chemistry.

to enrich different elements through centrifugation (Whittaker 1959). One of these fractions contained large quantities of organelles filled with synaptic vesicles. Under the electron microscope, it was shown that these were pinched off nerve terminals, and Whittaker named them *synaptosomes* (Gray and Whittaker 1962). The team was able to enrich vesicles from synaptosomes and to find that the neurotransmitter acetylcholine is stored in the vesicles.

After he was appointed director of the Neurochemical Department at the MPI for Biophysical Chemistry in 1973,[11] synaptosomes remained the most important resource in Whittaker's research. They enabled him to study the molecular processes during the uptake, storage, and release of neurotransmitters in the test tube. A majority of the experiments were now carried out on the electric organ of the fish *Torpedo marmorata*, a model system that—as opposed to the brains of mammals—has an exclusively cholinergic innervation as well as a thousand times more synaptic material than muscle tissue at the same weight. In order to get hold of enough electric fish for the research work, Whittaker set up a second laboratory at the Marine Station at Arcachon on the French Atlantic coastline (Whittaker 1989).

Whittaker and his colleagues were able to show that the neurotransmitters were not released from the cytoplasmic pool, but through fusion of the vesicle with the presynaptic membrane. They were also able to demonstrate that vesicles are "created" in the cell body and are then transported to the synapse in Fast Axonal Transport. Following vesicle fusion with the presynaptic membrane when the neurotransmitters are released, there is a reuptake of the vesicle, which is once again loaded with neurotransmitters. Whittaker and his colleagues studied this vesicle cycle with radioactive marker substances (e.g., Dextran) and with antibodies against specific proteoglycanes they had identified in the vesicle membranes. They also identified and localized other elements of the vesicle membrane. Figure 4 shows how far their knowledge had reached in the year 1984 (Whittaker 1984).

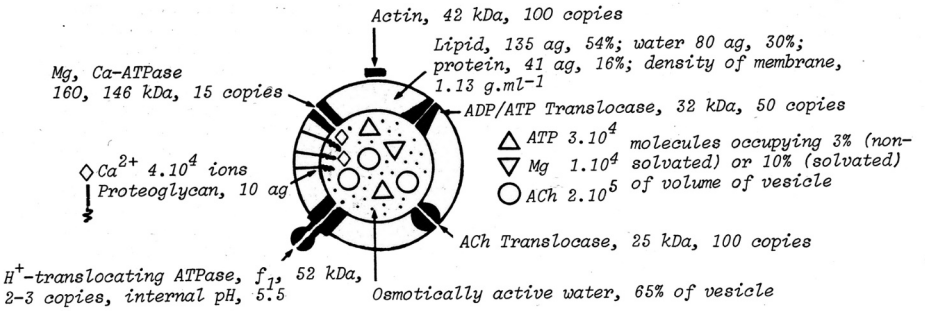

Figure 4. Schematic diagram of a synaptic vesicle. Shown here are the macromolecules associated with the vesicle membrane that were known in 1984, as well as the parts of the vesicle lumen (Whittaker 1984, Figure 13).

[11]Victor Whittaker was officially appointed in the first round on June 24, 1971, and in the second round on November 19, 1971, by the Senate of the Max Planck Society as a scientific member and director at the MPI for Biophysical Chemistry. See the minutes of the 69th session of the Senate from June 24, 1971, in Berlin, AMPG, II. Abt., Rep. 60, Nr. 69, as well as the minutes of the 70th session of the Senate from November 19, 1971, in Munich, AMPG, II. Abt., Rep. 60, Nr. 70.

Whittaker and his colleagues further elicited that, in the presynaptic plasma membrane, a high-affinity uptake system for choline exists that is blocked by snake poisons such as Alpha-Bungarotoxin. Another model system for the release of neurotransmitter substances established by Whittaker and his colleagues was the chromaffin cell from the adrenal medulla, whose vesicles, which are referred to as *granules*, are filled with catecholamines. The chromaffin cells are innervated by sympathetic nerve axons and release adrenaline or norepinephrine when excited. Elizabeth Fenwick (b. 1952), an Australian postdoctoral student, had developed a technique with which she was able to dissociate and enrich chromaffin cells (Fenwick et al. 1978). Whittaker and his coworkers then used these chromaffin cells to study the fusion of the granuli as a model for exocytosis (transporting substance out of the cell). They demonstrated that fusion is preceded by a multiple-stage process in which a network of proteins and specific detection mechanisms play an important role. As was to be shown later by Erwin Neher and his colleagues at the same institute, chromaffin cells were used successfully in patch clamp research (Fenwick, Marty, and Neher 1982).

Whittaker and his department at the MPI for Biophysical Chemistry were significantly involved in developing the field of neurochemistry in Germany. Several of the young researchers there were later appointed as professors at German universities (e.g., Heinz Breer, b. 1946, University of Stuttgart Hohenheim; Herbert Zimmermann, b. 1944, University of Frankfurt). At Whittaker's behest, a subgroup for neurochemistry was set up within the German Biochemistry Society. He organized regular meetings of this group, and the group's activities had a positive influence in promoting the cellular and molecular neurosciences in Germany.

Whittaker did the groundwork on the analysis of the synaptic vesicles and worked to clarify the complex biochemical and molecular network that leads to the release of neurotransmitters (Cowan and Kandel 2001). The Nobel Prize for Physiology or Medicine (2013)[12]—awarded to James E. Rothman (b. 1950) and Randy W. Schekman (b. 1948), and to Whittaker's earlier Ph.D. student in Göttingen, Thomas C. Südhof (b. 1955)—is also an acknowledgment of his pioneering achievements.

Department for Membrane Biophysics (1983–2011), Director: Erwin Neher

Erwin Neher studied physics and completed his Ph.D. in 1970 at the MPI for Psychiatry in Munich under Hans-Dieter Lux (1924–1994). He had already investigated nerve cells in his Ph.D. thesis titled, "The Dynamic Properties of Nerve Soma Membranes," applying the current clamp method with specially developed microelectrodes and electronic amplifiers (Neher 1970). In 1972, Neher moved to the MPI for Biophysical Chemistry, joining the Department of Molecular Systems Assembly (under Director Hans Kuhn, 1919–2012; see Eichele 2012), where he initially researched into ion channels in artificial membranes using noise and fluctuation analysis.

When in 1973, Bert Sakmann, who had done his thesis under Creutzfeldt in Munich, came to Creutzfeldt's department in Göttingen after a three-year period of research under Bernard Katz (1911–2003) (Katz 1996; Sakmann 2007; Stahnisch 2017) in London, England, Neher and Sakmann began working together (Neher 1992a; Sakmann 1992a). The two knew

[12]See https://www.nobelprize.org/prizes/medicine/2013/press-release/ (accessed May 27, 2020).

one another well from their time in Munich (MPI for Psychiatry). Sakmann had studied the neuromuscular synapses in Bernard Katz's laboratory, and he brought this experimental system into the joint research project, whereas Neher contributed his expertise on measuring ion channels in membranes. They were the first in the world to register the single channels in the membrane of muscle cells, which are controlled by the neurotransmitter acetylcholine, using microelectrodes (Figure 5; see Neher and Sakmann 1976).

Because of these important results, in 1976 a Young Investigators Laboratory was set up for Neher and Sakmann at the Göttingen Institute and, in 1979, the Membrane Biology Research Group was established, together with Francisco J. Barrantes (b. 1944) from the department for Molecular Biology of Thomas Jovin (b. 1939; see Niemann 2020). Barrantes, Neher, and Sakmann were now able to realize their own research projects on a larger scale. The group's common ground was researching the nicotinic acetylcholine receptor (nAchR), which is expressed in the neuromuscular synapse and—in high density—in the electrical organ of the *Torpedo marmorata*. Barrantes studied the binding properties, the kinetics, and the structure of nAchR using biophysical methods (Barrantes 1983), whereas Sakmann and Neher continued to research the channel properties of nAchR using microelectrodes.

Although in the early experiments (Figure 5), the signal/noise ratio of their measurements was not yet ideal, Neher, Sakmann, and their colleagues managed to considerably improve this so-called patch clamp technique, developing it to become the most important instrument in modern neurophysiology (Reyes 2019). The corresponding publication (Hamill et al. 1981) has been cited more than 18,000 times to date.[13] Neher, Sakmann, and their colleagues initially studied the physiological properties of nAchR and the Na^+ channels together, but at some point they began pursuing their own different research interests. Whereas Sakmann concentrated on the

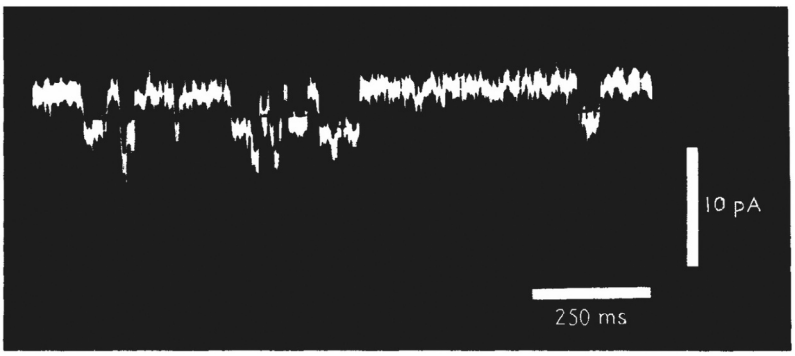

Figure 5. Oscilloscope recording of current through a patch of membrane of approximately 10 μm^2. Downward deflection of the trace represents inward current. The pipette contained 2 x 10^{-7} M suberyldichlorine in Ringer's solution. The experiment was carried out with a denervated hypersensitive frog (*Rana pipiens*) cutaneus pectoris muscle in normal frog Ringer's solution. The record was filtered at a bandwidth of 200 Hz. Membrane potential: −120 mV. Temperature: 8°C (Neher and Sakmann 1976, Figure 2).

[13]See https://apps.webofknowledge.com/full_record.do?product=WOS&search_mode=GeneralSearch&qid=1&SID=C6sNCFVQOdB5G9NRJ6j&page=1&doc=1 (accessed May 30, 2020).

postsynaptic neurotransmitter receptors, Neher chose the release of neurotransmitters from the presynaptic side as his research focus. In 1991, they received the Nobel Prize for Physiology or Medicine for their discovery of the function of single membrane channels in nerve cells (Neher 1992b; Sakmann 1992b).

Erwin Neher was appointed director of the Department for Membrane Biophysics in 1983.[14] Following that, his laboratory predominantly studied the role of Ca^{2+} in the release of neurotransmitters at synapses and in the secretion of catecholamines from chromaffin cells. The fact that the latter was used as a model system, was a stroke of luck, as described above. Elizabeth Fenwick had dissociated chromaffin cells on a large scale and, when Neher and his former colleague Alain Marty (b. 1949) were looking for "small" test cells for their patch clamp recordings around 1981, they used Fenwick's cells for this (Fenwick, Marty, and Neher 1982). Like nerve cells, chromaffin cells demonstrated acetylcholine sensitivity and had Na^{+} and Ca^{2+} channels as well as secretory vesicles. For many years, they remained the "standard cell type" in Neher's department (Neher 2018).

Neher and his colleagues were successful in further developing the patch clamp technique, and they were able to verify the fusion of vesicles with the cell membrane using capacitance measurement. Moreover, they filled the chromaffin cells with Ca^{2+} indicators (e.g., Fura-2) and this allowed them to optically measure the intracellular Ca^{2+} concentration.[15] They used "caged Ca^{2+}," which is released through photolysis, to change the intracellular Ca^{2+} concentration quickly, and they were ultimately able to measure the

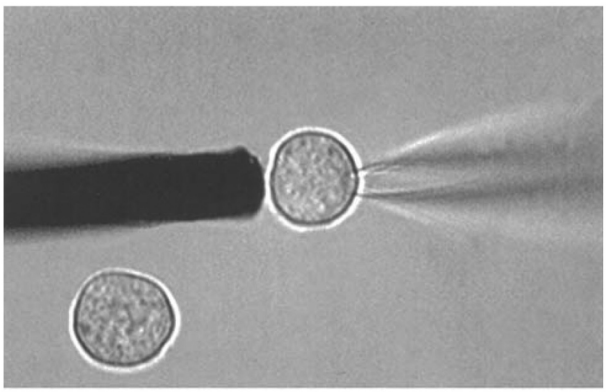

Figure 6. Techniques to monitor exocytosis in adrenal chromaffin cells. Two chromaffin cells are shown and a microcarbon fiber (left) is touching one of them, which is also under whole-cell patch clamp (right). The cell is filled with caged-Ca^{2+} which can be released by a light flash. The cell is also filled with a Ca^{2+}–indicator to measure the internal Ca^{2+}concentration (Neher 2006, Figure 1).

[14]Erwin Neher was officially appointed in the first round on November 19, 1982, and in the second round on March 3, 1983, by the Senate of the Max Planck Society as a scientific member and director at the MPI for Biophysical Chemistry. See the minutes of the 103rd session of the Senate from November 19, 1982, in Munich, AMPG, II. Abt., Rep. 60, Nr. 103., as well as the minutes of the 104th session of the Senate from March 11, 1983, in Stuttgart, AMPG, II. Abt., Rep. 60, Nr. 104.

[15]Fura-2 is a fluorescent Ca^{2+} indicator. The principle using Fura-2 is based on the shift of its fluorescence excitation upon Ca^{2}-binding.

release of catecholamines using a carbon microelectrode. By applying these four extremely complex and complementary methods (Figure 6), Neher and his colleagues were able to decipher the role of Ca^{2+} in vesicle release.

They demonstrated what role is played by the influx of Ca^{2+} through the cell membrane, and they described the release of Ca^{2+} out of intracellular reservoirs and the regulation of this reservoir by second messengers. Although chromaffin cells provide an excellent model system for the vesicular release of neurotransmitters, there are nevertheless differences in comparison to the much faster synaptic release in nerve cells (Neher 2006). At the active zone of the synapse (see Figure 3), the release of the vesicle is accelerated by a network of proteins: the so-called SNARE complex (SNARE: SNAP attachment receptor; SNAP: soluble NSF attachment protein; NSF: *N*-ethylmaleimide-sensitive–factor).

In Neher's laboratory, the "Calyx of Held"—a giant synapse from the auditory system in the brain stem—initially served as a model for the release of the neurotransmitter glutamate (Schneggenburger and Neher 2000). Later on, Neher and his colleagues also studied the neurotransmitter release on other synapses of the brain (medial septum, hippocampus) and, in addition to "normal" neurotransmitter release, they studied their plastic changes, which presumably play a role in learning and memory.

In cooperation with Reinhard Jahn (b. 1950, MPI for Biophysical Chemistry) and Nils Brose (b. 1962, MPI for Experimental Medicine), the group surrounding Neher has decoded the physiological role of several proteins (e.g., SNAP–25, MUNC 13: Mammalian uncoordinated protein 13) in the release of the synaptic vesicles. Thanks to the work of the departments of Brose, Jahn, and Neher, Göttingen became a worldwide leading center in this area—although the fact that German-American biochemist Thomas C. Südhof only remained director at the MPI for Experimental Medicine for a brief period (1995–1998) is regrettable.

During his almost 40 years of research at the MPI for Biophysical Chemistry, Neher gave many young scientists, in his unassuming and unselfish way, the chance to develop their own research profile and thus to launch their own careers. The early colleagues Owen Hamill (b. 1949), Alain Marty, and Frederick J. Sigworth (b. 1951) became professors in Galveston, Paris, and Yale, respectively. Wolfhard Almers (b. 1943) was a visiting researcher under Erwin Neher as a Humboldt Research Fellow and, in 1991–1992, he became director at the MPI for Medical Research in Heidelberg.[16]

Later on, Neher and the other directors of the institute promoted the following young scientists as the heads of independent Young Investigator Groups at the MPI for Biophysical Chemistry: Walter Stühmer (b. 1948, since 1992 director at the MPI for Experimental Medicine),[17] Andreas Karschin (b. 1958, from 2001–2008 professor of neurophysiology, University of Würzburg), Christian Rosenmund (b. 1965, since 2009 professor of neurophysiology, Charité Berlin), Ralf Schneggenburger (b. 1964, since 2005

[16]Wolfhard Almers was officially appointed in the first round on November 15, 1990, and in the second round on March 8, 1991, by the Senate of the Max Planck Society as a scientific member and director at the MPI for Medical Research. See the minutes of the 126th session of the Senate from November 15, 1990, in Munich, AMPG, II. Abt., Rep. 60, Nr. 126. SP, as well as the minutes of the 127th session of the Senate from March 8, 1991, in Frankfurt/M, AMPG, II. Abt., Rep. 60, Nr. 127.

[17]Walter Stühmer was appointed as director on March 13, 1992, in the first and on June 4, 1992, in the second round by the Senate of the Max Planck Society as a scientific member at the MPI for Experimental Medicine in Göttingen, and as a director. See the minutes of the 130th session of the Senate from March 13, 1992, in Munich, AMPG, Abt. II, Rep. 60, Nr. 130, as well as the minutes of the 131st session of the Senate from April 6, 1992, in Dresden, AMPG, Abt. II, Rep. 60, Nr. 131.

professor at EPFL Lausanne), Stefan Sigrist (b. 1967, since 2008 professor of genetics, Free University Berlin), Takeshi Sakaba (b. 1972, since 2011 professor of neurosciences, Doshisha University, Japan), Jürgen Klingauf (b. 1967, since 2008 professor of biophysics, University of Münster), and Dirk Fasshauer (b. 1965, since 2010 professor of cell biology, University of Lausanne).

Over a period of many years, Neher worked to bring about an increase and an improvement to the promotion of research by the European Community. He managed, for example, to set up the European Neuroscience Institute (ENI) in Göttingen as a European project in 2000, together with Diethelm W. Richter (b. 1943, University of Göttingen) and Walter Stühmer (MPI for Experimental Medicine). At the present time, seven Young Investigator Groups are working in different fields of the neurosciences at the ENI.[18] Since 2011, Neher has been an emeritus director and continues to study the role of Ca^{2+} ions in the release of neurotransmitters in synapses.[19]

Department of Cell Physiology (1985–1989), Director: Bert Sakmann

Bert Sakmann[20] and Erwin Neher developed the patch clamp technique together at the end of the 1970s. At the beginning of the 1980s, their research interests took different paths, and Sakmann and his colleagues concentrated on the neurotransmitter-driven ion channels in postsynaptic membranes. At first, they primarily studied the neuromuscular synapses and the ion channels that are driven by the neurotransmitter acetylcholine (nAchR; see Sakmann 1992b). Later, Sakmann and his colleagues also studied the inhibitory synaptic transmission between nerve cells in dissociated neurons of the medulla, whereby glycine and γ-amino-butyric acid (GABA) are released as neurotransmitters. When glycine or GABA are bound to the corresponding receptors in the postsynaptic membrane (GlyR, GABAR), this results in an influx of Cl^- ions and therefore in the inhibition of the postsynaptic cells (Bormann, Hamill, and Sakmann 1987).

When, between 1982 and 1984, the Japanese biochemist Shosaku Numa (1929–1992), together with his colleagues in Kyoto, cloned, sequenced, and espressed the cDNA of nAchR in Xenopus oocytes (Mishina et al. 1984), this saw the beginning of a highly fruitful cooperation between Sakman's und Numa's laboratories.[21] It was no doubt of some advantage that Numa had worked for a total of eight years between 1958 and 1968 with the Nobel laureate Feodor Lynen (1911–1979) at the MPI for Cell Biology in Munich (Sakmann 1992c). Sakmann, his colleague Christoph Methfessel (b. 1951), and the Numa group succeeded in removing the vitelline membrane (yolk sac) of the oocytes, and they were ultimately able to study the expressed ion channels using patch clamp electrodes on the plasma membrane (Sakmann et al. 1985). They found that regulation of the different subunits of the nAchR is development-dependent: In fetal receptors, the γ-subunit is incorporated; in adult receptors, there is an exchange with the ε-subunit. Accordingly, the ion currents through the channels gated by the receptors are changed.

[18]See http://www.eni.gwdg.de/home/about-the-institute (accessed May 27, 2020).
[19]Membrane Biophysics emeritus group at https://www3.mpibpc.mpg.de/groups/neher/ (accessed May 28, 2020).
[20]Bert Sakmann was appointed by the Senate of the Max Planck Society on June 9, 1983, as a scientific member at the MPI for Biophysical Chemistry. See the minutes of the 105th session of the Senate from June 9, 1983, in Saarbrücken, AMPG, II. Abt., Rep. 60, Nr. 105.
[21]For more details on the cooperation between Sakmann and Numa, see Sakmann and Stahnisch (2021).

Numa and his colleagues modified the amino acids residues of the nAchR subunits that coat the channel using site directed mutagenesis, and Sakmann and his colleagues measured the corresponding ion currents after expression in oocytes (Imoto et al. 1988). This enabled them to establish for the first time a molecular structure–function relationship for ligand-controlled ion channels. This fruitful cooperation between Kyoto, Japan, and Göttingen was intensified when Veit Witzemann (b. 1945) spent some time researching in Kyoto, which also served to provide Göttingen with molecular know-how that enabled physiological studies of nAchR composed of different combinations of subunits (Witzemann et al. 1990).

After the Numa group had also cloned the voltage-gated Na^+-channel and the K^+-channel of the nerve cell membrane, it was mainly Walter Stühmer who studied the functional properties of these channels in expression models in Göttingen. Whereas patch clamp recordings had only been possible in isolated cells up to that time, in 1988, Sakmann's department achieved patch clamp recordings of neurons of the CNS *in situ* for the first time (Edwards et al. 1989). This technique revolutionized neurophysiological examinations of neurons of the CNS, and Sakmann and his colleagues went on to carry out ground-breaking research on neurons of the cortex. However, this was no longer done in Göttingen, but in Heidelberg, as Sakmann was appointed director at the MPI for Medical Research in Heidelberg in 1988.[22] He was convinced that cooperation between neurophysiologists and molecular biologists was necessary in order to understand synaptic transmission in the CNS. The Center for Molecular Biology in Heidelberg (ZMBH) offered the chance to bundle such strengths, and Sakmann did indeed manage, mainly in cooperation with Peter Seeburg (1944–2016) from the ZMBH, later also at the MPI for Medical Research,[23] to considerably advance our understanding of the synaptic circuitry in the brain (Wisden 2016).

Department for Neurobiology (1997–2018), Director: Reinhard Jahn

Reinhard Jahn studied biology and chemistry in Freiburg and Göttingen and completed his Ph.D. in 1981 at the Institute for Clinical Biochemistry at the University of Göttingen under Hans-Dieter Söling (1929–2006). He had studied secretory cells and exocytose while still working on his Ph.D. (Jahn 1981). He completed a postdoctoral training course from 1983 to 1986, followed by an assistant professorship under Paul Greengard (1925–2019), first at Yale University and then at Rockefeller University.[24] During this time he began—together with Thomas Südhof and Pietro de Camilli (b. 1947)—to systematically search for proteins that are integrated into the membrane of synaptic vesicles. In 1985, he succeeded in identifying the protein p38, later given the name *synaptophysin* (Jahn et al. 1985). After returning to Germany, Jahn headed a Young Investigators Group on Structure and Function of Synaptic Vesicles from 1986 to 1991 at the MPI for Psychiatry in Martinsried

[22]Following various preliminary negotiations with the MPI for Systems Physiology in Dortmund and the MPI for Biophysics in Frankfurt am Main, he was appointed a scientific member and director at the MPI for Medical Research on June 11, 1987, at a formal session of the Senate of the Max Planck Society. See the minutes of the 116th session of the Senate from June 11, 1987, in Hamburg, AMPG, II. Abt., Rep. 60, Nr. 116.

[23]Following an appointment to Munich's MPI for Psychiatry, which he turned down in 1991, Peter Seeburg was formally appointed to the MPI for Medical Research on November 18, 1994. See the minutes of the 138th session of the Senate from November 18, 1994, in Frankfurt/M, AMPG, II. Abt., Rep. 60, Nr. 138.

[24]See https://www.mpibpc.mpg.de/51667/cv_Jahn (accessed May 27, 2020).

(Max-Planck-Gesellschaft 1992, 190). There, he and his colleagues discovered the vesicle proteins synaptobrevin and rab3 (Ras related in brain 3; Ras: rat sarcoma; see Baumert et al. 1989).

The early 1990s were the "golden years" for the discovery of proteins, which play a decisive role in binding vesicles to the outer cell membrane and in the subsequent fusion and secretion (Südhof 2014). Three groups made significant contributions here, with different model systems and working methods. James E. Rothman and colleagues studied intracellular vesicle transport in a cell-free assay with the biochemical method. They found NSF, SNAP, and named the proteins that are involved in binding the vesicle to the cell membrane the SNARE complex (Söllner et al. 1993). Randy W. Schekman and his colleagues used genetic screens to study yeast mutants in which the secretion was impaired. They cloned the corresponding gene and discovered the biochemical reactions that play a role in secretion. Thomas C. Südhof, Pietro de Camilli, and Reinhard Jahn researched the proteins that control the fusion of the vesicles with the cell membrane in nerve cells, contributing to the release of neurotransmitters using biochemical, genetic, physiological, and electron-microscopic methods. All three groups discovered similar proteins and mechanisms, which shows that secretion is an evolutionarily old and conserved mechanism (Bennett and Scheller 1993).

The Max Planck Society, unfortunately, could not offer Jahn an adequate position after his post as head of the Junior Investigators Group in Munich expired, and he returned to the United States. There, he was at the Yale University School of Medicine from 1991 to 1997, his last position being professor of pharmacology and cell biology. During this time, he made important contributions toward identifying synaptotagmin (previously P65) as a Ca^{2+} sensor in the release of neurotransmitters (Brose et al. 1992). He was also able to demonstrate how neurotoxins like tetanus toxin or botulinum toxin inhibit the release of neurotransmitters by interacting with synaptobrevin, syntaxin, or SNAP 25 (Blasi et al. 1993). In 1995, Jahn was appointed a scientific member and director of the Department for Neurobiology at the MPI for Biophysical Chemistry, taking up his work in Göttingen in 1997.[25]

The phase of discovering new proteins was then followed by research into the mechanisms by which these proteins enable vesicles to fusion with the cell membrane. The original model by Rothman and his colleagues assumed that the SNARE proteins had an antiparallel configuration. Jahn, John E. Heuser (b. 1942), and colleagues proved using cryo-electron microscopy that they had a parallel configuration (Hanson, Heuser, and Jahn 1997). They presented the hypothesis that the fusion of the vesicles with the cell membrane takes place via the binding of the SNARE proteins in a similar way to a zip (*zippering hypothesis*). Jahn and his colleagues later corroborated this hypothesis by carrying out an x-ray structure analysis of the SNARE complex (Figure 7; see Stein et al. 2009; Sutton et al. 1998).

[25]Reinhard Jahn was appointed to the MPI for Biophysical Chemistry as a scientific member and director on March 24, 1995, in the first round and on June 22, 1995, in the second round by the Senate of the Max Planck Society. See the minutes of the 139th session of the Senate from March 24, 1995, in Berlin, AMPG, II. Abt., Rep. 60, Nr. 139, as well as the minutes of the 140th session of the Senate from June 22, 1995, in Potsdam, AMPG, II. Abt., Rep. 60, Nr. 140.

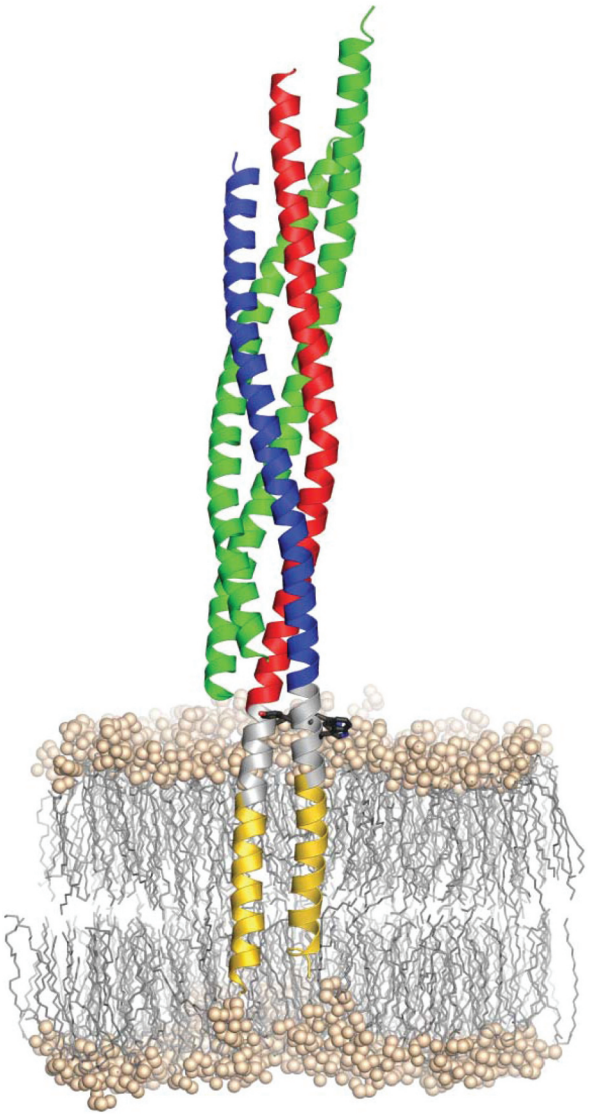

Figure 7. Model of the synaptic SNARE complex inserted in a membrane (Stein et al. 2009, Figure 4).

Jahn and his colleagues were also able to show that SNARE proteins can lead to membrane fusion when integrated into artificial membranes. Due to this groundbreaking work, the zipper model has become the generally accepted structural model for the SNARE complex and vesicle fusion (Südhof 2014).

Jahn and his coworkers have also investigated the structure and function of the vesicles themselves (Figure 8). They have determined and analyzed vesicular transmitter transporters (Takamori et al. 2000). They were the first to prove the uptake of GABA in vesicles; they were able to solve the energy balance of the transport and to show that GABA, glycine, and glutamate are stored in the vesicles. They also succeeded in developing a structural and quantitative model of the synaptic vesicles (Takamori et al. 2006).

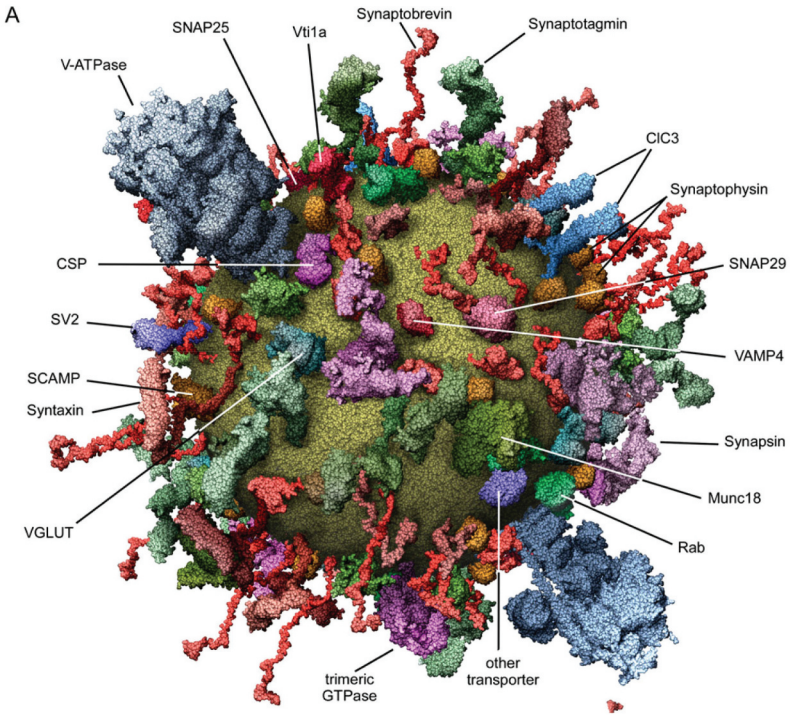

Figure 8. Molecular model of an average synaptic vesicle showing the macromolecules inserted into the vesicle membrane. The model is based on space-filling models of all macromolecules at near atomic resolution and shows an outside view of a vesicle (Takamori et al. 2006, Figure 4A).

In addition to his research activities, Reinhard Jahn has actively promoted young scientists and research in Göttingen. He was for many years the scientific supervisor of the Graduate Center for Neurosciences, Biophysics, and Molecular Biosciences. He was a cofounder of the Ph.D. program in molecular biology and the neurosciences program. He contributed to the success of Göttingen University in the Excellence Initiative. He was the spokesman of the Max Planck Society Research School for Molecular Biology and coordinator of the EU-funded Marie Curie Training Program. He also spent many years working for the European Research Council and the German Research Foundation (DFG) on important committees. Jahn retired as department head in 2018, but he continues to conduct research within the framework of an emeritus group in Göttingen that was established for him by the MPG.[26]

Conclusions

The two first appointed neuroscientists of the MPI for Biophysical Chemistry, Otto Creutzfeldt and Victor Whittaker, were already internationally renowned personalities when they moved to Göttingen and successfully continued their research. In retrospect, however, the real success of these appointments lies in the fact that they became a hotbed of young talent, whose second generation made Göttingen one of the world's top centers of

[26]Laboratory for Neurobiology, MPI for Biophysical Chemistry. Jahn is currently president of the University of Göttingen. See https://www.mpibpc.mpg.de/jahn (accessed May 28, 2020).

basic neuroscience research. It was also a sanctuary in the sense that young talents were granted a grace period; Sakmann and Neher were able to develop and perfect the patch clamp method over several years, well funded, without the pressure to publish and without having to write research proposals. The next steps were the Young Investigators Lab and the Membrane Biology Research Group established for Barrantes, Neher, and Sakmann. Neher and Sakmann were appointed scientific members of the MPG and heads of department in 1983 and 1985, respectively, whereas Barrantes returned to his native Argentina in 1983 and became director of the Institute for Biomedical Research in Bahia Blanca.[27]

Another example of such promotion of young talents—also at the MPI for Biophysical Chemistry, albeit not in the neurosciences—is the support of Stefan Hell (b. 1962) by then Managing Director Thomas Jovin. Hell was researching a new method to overcome the resolution limit in light microscopy. Jovin, who himself had made important contributions to microscopic imaging, convinced his fellow directors at the institute to set up a small microscope research group.

Hell was able to bring his ideas to fruition as head of an Independent Junior Research Group at the institute from December 1996 onward and was appointed head of department and director in 2002. In 2014 he received the Nobel Prize in Chemistry for the development of stimulated emission depletion (STED) microscopy.[28] One of the first applications of STED microscopy was the visualization of vesicles in synapses, a common project of Stefan Hell and Reinhard Jahn (Willig et al. 2006). Independent Junior Research Groups as a tool to promote young scientists have been instituted in the MPG since 1969, when the first four groups were established in the Friedrich-Miescher-Laboratory in Tübingen[29]; currently, more than 150 such research groups are working in the MPG.[30]

In Göttingen, cooperation between the Georg-August-University and the Max Planck Institutes has been fostered through joint Graduate Centers for Neurosciences, Biophysics, and Molecular Biosciences. In addition, a course of study in neurosciences was introduced, in which members of the Max Planck Institutes also took on teaching duties. As mentioned above, Reinhard Jahn was particularly active in these initiatives.

An important reason for close cooperation of Max Planck Institutes and universities are joint programs for research funding, such as Collaborative Research Centers (CRC) of the German Research Foundation (DFG), obtaining grants from the European Union, and, more recently, the Excellence Initiative of the Federal Ministry of Education and Research (BMBF). Of the 10 CRCs currently funded by the DFG at the University of Göttingen, two have their main focus in the neurosciences. In CRC 1286, "Quantitative Synaptology," 24 subprojects from the University of Göttingen and the Max Planck Institutes combine their research on the molecular structure and function of synapses.[31] In CRC 889, "Cellular Mechanisms of Sensory Processing," 21 groups from the University of Göttingen, the German Primate Center, and various Max Planck Institutes are working together to decipher the mechanisms of sensory perception from the receptor to the brain.[32] In the BMBF Excellence Initiative, the University of Göttingen received a Cluster of Excellence on

[27]See https://twas.org/directory/barrantes-francisco-jose (accessed May 30, 2020).
[28]See https://www.nobelprize.org/prizes/chemistry/2014/hell/biographical/ (accessed May 28, 2020).
[29]Minutes of the 62nd session of the Senate from March 7, 1969, in Frankfurt–Höchst, AMPG, II. Abt., Rep. 60, Nr. 62.
[30]Annual Report of the MPG (2019): 136–145.
[31]See https://www.sfb1286.de (accessed May 28, 2020).
[32]See www.sfb889.uni-goettingen.de (accessed May 28, 2020).

"Multiscale Bioimaging: From Molecular Machines to Networks of Excitable Cells," which aims to understand the structural and resulting functional properties of excitable cells in the heart and brain over several length scales. The Max Planck Institutes make an important contribution to the research program of this cluster.[33]

As briefly mentioned, in 2000 the European Neuroscience Institute (ENI) was founded in Göttingen. The ENI is jointly financed by the University of Göttingen and the Max Planck Society and currently offers seven young scientists the opportunity for independent research in an institute building built in 2006 on the university campus. ENI–Göttingen is the nucleus of an international network of 15 ENI institutes in 10 European countries that promote independent junior research groups in the field of neurosciences. There is a lively exchange between these institutes in the form of annual meetings and workshops, as well as an exchange of doctoral students, which is financially supported by the European Union.[34]

The example of the Goettingen MPI for Biophysical Chemistry presented here highlights essential features in a concluding remark of how neuroscientific research has been organized in the MPG:

(1) During the early 1950s, the consolidation of the two "classical" neuroscience institutes —the MPI for Brain Research (Gießen, Frankfurt) and the MPI for Psychiatry (Munich)[35]—was given the highest priotity by the MPG. Research in the two institutes continued along the groundwork already laid in the Kaiser Wilhelm Society with a clear medical and disease oriented focus. The consolidation period followed the establishment of two new neuroscience institutes: the MPI for Behavioral Physiology (1954, Seewiesen)[36] and the MPI for Biological Cybernetics (1968, Tübingen).[37] Both of these "new" MPIs were founded because two novel, interesting, and promising themes of research showed up and outstanding scientists were available as founding members. All four institutes were relatively small (up to four departments) and their research had a clear focus. The establishment of the MPI for Biophysical Chemistry followed a different motive and was implemented on a much larger scale: Eleven department were assembled in order to explore the physical, chemical, and biological basis of complex living systems, and among them, two concentrated on neuroscience.[38] In the new institute bridges were built from molecular biology to cell biology, from laser physics to spectroscopy, from magnetic resonance imaging to X-ray diffraction, and the neuroscientists could make use of all these technologies.

(2) Since the 1940s and 1950s, the time of chemists and physicists in biology and medicine had dawned globally. And here in the example of Göttingen we see how this trend continued in the neurosciences that were becoming established. In Goettingen's day-to-day research, the teams, although tending to be open to theoretical neurobiology, mainly followed the logic of technology-based laboratory and

[33]See https://www.mpibpc.mpg.de/16497889/pr_1825 (last accessed on May 28, 2020).
[34]See www.eni.gwdg.de (accessed May 28, 2020).
[35]See also the contributions by Florian Schmaltz and Lisa Malich in this Special Issue of the *Journal of the History of the Neurosciences*, forthcoming (2022).
[36]Minutes of the 17th session of the Senate on January 29, 1954, in Düsseldorf, AMPG, II. Abt., Rep. 60, Nr. 17. See also Kaufmann (2018).
[37]Minutes of the 60th session of the Senate on June 27, 1968, in Mainz, AMPG, II. Abt., Rep.60, Nr. 60. See also Sascha Topp, "Biocybernetics Approaches in Max Planck Institutes in the Postwar Era: A Contribution to the History of Research Clusters in Neuroscience" in *Journal of the History of the Neurosciences*, forthcoming, 2022.
[38]Minutes of the 67th sessioin of the Senate from November 24, 1970, in Stuttgart, AMPG, II. Abt., Rep. 60, Nr. 67.

workshop environments. Scientific methods dominated. Research approaches in the humanities tended to be promoted at other MPG sites.

Although approaches of pathology up to neurotoxins were used in models, the MPIs working in neuroscience had increasingly placed themselves under a basic science research agenda since the 1970s. They did not primarily seek possible medical applications anymore. Using artificial and natural model systems (cells, membranes, animals), scientists in Göttingen tended to pursue experimental neuroscience, which was intended to contribute to the understanding of structure and function. Particularly, to elucidate signaling by neurotransmitters, it was necessary to think in terms of complex biochemical and molecular "networks." As elsewhere in neuroscience, the choice of model was crucial for gaining knowledge; be it "classically," with animal experiments in neurophysiology and neurochemistry, or chromaffin cells in membrane research and cell biology. Classical visualization strategies such as light and electron microscopy and perfected (noise) fluctuation analyses by means of microelectrode recordings were applied in addition to modern molecular biological methods.

(3) Within the Goettingen departments, a significantly growing number of small, high-performing teams—typically consisting of three or four international members—were supported to pursue research problems, undisturbed and technically well equipped. Here, the style of personalities like Creutzfeldt and Whittaker created a positive environment, including incentives for autonomously conducted research. All of that resulted in a series of breakthroughs in modern neuroscience and technology (e.g., patch clamp recording and STED microscopy). At the same time, this novel concentration of personnel, know-how, and research infrastructure favored a growing connectedness on several levels. The Göttingen site developed into an international research center. This local cluster for neurobiology—now becoming a hub like Martinsried (biomedicine) or Heidelberg (molecular biology)—has been based on the collaboration of several departments of two MPIs with the university, jointly attracting national and European research funding. The recent decision by the MPG to merge the MPI for Experimental Medicine and the MPI for Biophysical Chemistry will further strengthen the Göttingen cluster of neurobiology.

Authorship note

Heinz Wässle conceived the article and elaborated all of its essential parts. Sascha Topp supplemented the contribution with comments, historical sources, and literature. Our discussions resulted in a series of adaptations as well as a joint summary of the results.

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ORCID

Sascha Topp http://orcid.org/0000-0001-7235-8747

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