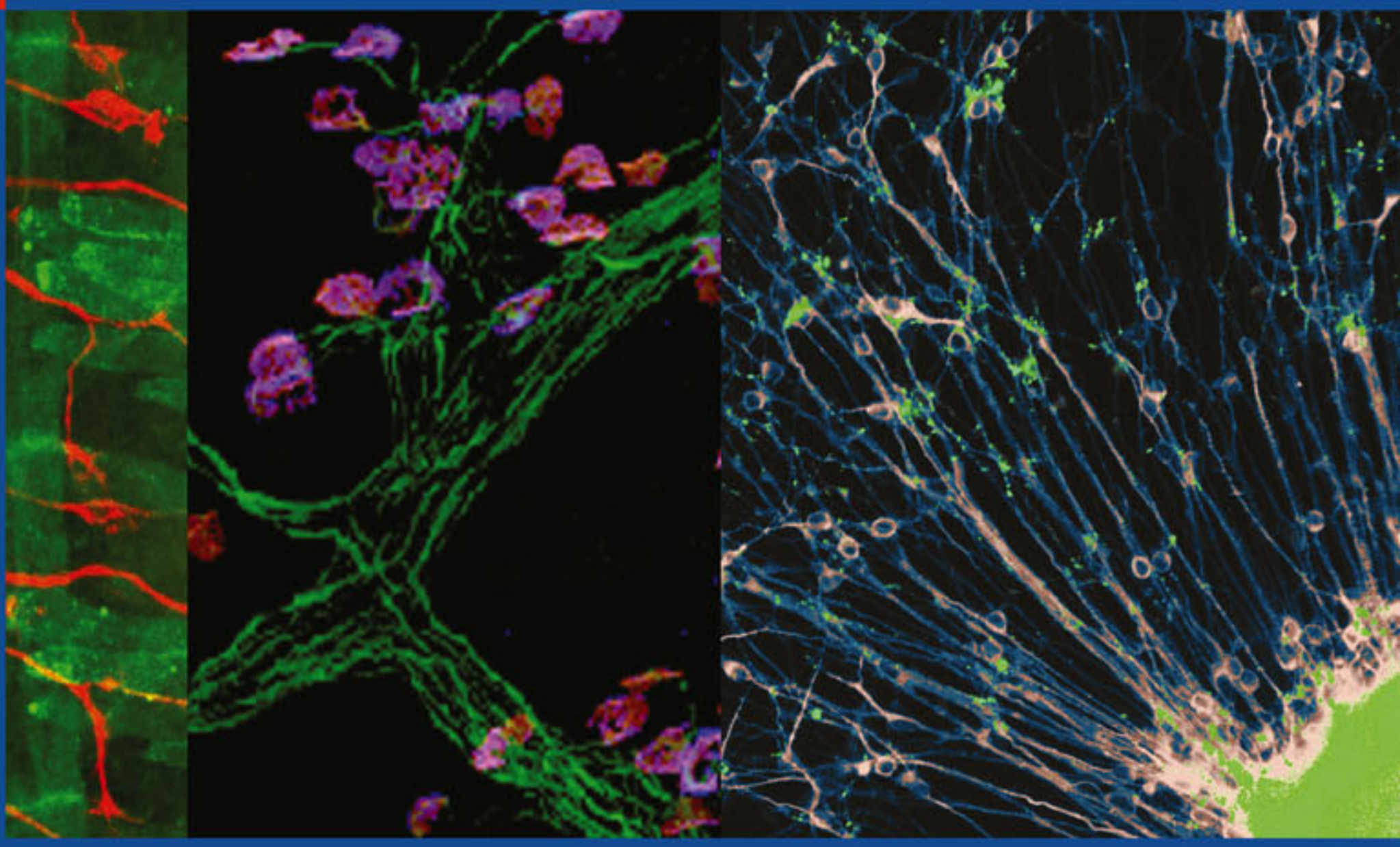
Michael Hortsch • Hisashi Umemori

Editors

The Sticky Synapse

Cell Adhesion Molecules and Their Role in Synapse Formation and Maintenance



Springer

The Sticky Synapse

Michael Hortsch · Hisashi Umemori
Editors

The Sticky Synapse

Cell Adhesion Molecules and Their Role in Synapse Formation and Maintenance

Springer

Editors
Michael Hortsch
Department of Cell & Developmental Biology
University of Michigan
Medical School
109 Zina Pitcher Place
Ann Arbor MI 48109
Biomedical Sciences
Research Bldg.
USA
hortsch@umich.edu

Hisashi Umemori
Molecular and Behavioral Neuroscience Institute and Department of Biological Chemistry
109 Zina Pitcher Place
Ann Arbor, MI 48109
USA
umemoh@umich.edu

Cover illustrations: Developing Synapses - Synapses are formed at points of contact between axons and their targets. From left, Drosophila neuromuscular junctions (motor axons, red; muscles, green), mouse neuromuscular junctions (motor axons, green; neuromuscular junctions, pink), and mouse cerebellar synapses in culture (pontine axons, blue; cerebellar granule cell dendrites, pink; synapses, green).
Courtesy of Carrero-Martinez and Chiba (Drosophila) and Harris and Umemori (mouse).

ISBN 978-0-387-92707-7 e-ISBN 978-0-387-92708-4
DOI 10.1007/978-0-387-92708-4
Springer Dordrecht Heidelberg London New York

Library of Congress Control Number: 2009929373

© Springer Science+Business Media, LLC 2009
All rights reserved. This work may not be translated or copied in whole or in part without the written permission of the publisher (Springer Science+Business Media, LLC, 233 Spring Street, New York, NY 10013, USA), except for brief excerpts in connection with reviews or scholarly analysis. Use in connection with any form of information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed is forbidden. The use in this publication of trade names, trademarks, service marks, and similar terms, even if they are not identified as such, is not to be taken as an expression of opinion as to whether or not they are subject to proprietary rights.
While the advice and information in this book are believed to be true and accurate at the date of going to press, neither the authors nor the editors nor the publisher can accept any legal responsibility for any errors or omissions that may be made. The publisher makes no warranty, express or implied, with respect to the material contained herein.

Printed on acid-free paper

Springer is part of Springer Science + Business Media (www.springer.com)

Preface

The molecular mechanisms, which are responsible for the functional differences between the various types of neuronal synapses, have become one of the central themes of modern neurobiology. It is becoming increasingly clear that a misregulation of synaptogenesis and synaptic remodeling and dysfunctional neuronal synapses are at the heart of several human diseases, both neurological disorders and psychiatric conditions. As synapses present specialized cellular junctions between neurons and their target cells, it may not come as a surprise that neural cell adhesion molecules (CAMs) are of special importance for the genesis and the maintenance of synaptic connections. Genes encoding adhesive molecules make up a significant portion of the human genome, and neural CAMs even have been postulated to be a major factor in the evolution of the human brain. These are just some of the many reasons why we thought a book on neural CAMs and their role in establishing and maintaining neuronal synapses would be highly appropriate for summarizing our current state of knowledge. Without question, over the near future, additional adhesive proteins will join the ranks of synaptic CAMs and our knowledge, and how these molecules enable neurons and their targets to communicate effectively will grow. We hope that this book will provide a comprehensive and timely synopsis of the role of CAMs at synaptic connections and will encourage other researchers to join this exciting field of neuroscience, which has the promise not only to yield new insights into the functioning of our brain but also to shed light on some devastating human diseases.

Michael Hortsch
Ann Arbor, MI Hisashi Umemori

Contents

Contributors

Michael V.L. Bennett Dominick P Purpura Department of Neuroscience, Albert Einstein College of Medicine, 1410 Pelham Parkway South, Room 704, Bronx, NY 10804, USA, mbennett@aecom.yu.edu

Laurent Bogdanik The Jackson Laboratory, 600 Main St., Bar Harbor, ME 04609, USA, laurent.bogdanik@jax.org

Thomas Bourgeron Human Genetics and Cognitive Functions Unit, Department of Neuroscience, Institut Pasteur, 25 rue du Docteur Roux, 75724 Paris Cedex 15, France, thomasb@pasteur.fr

Mario Rosario Buffelli Dipartimento di Scienze Neurologiche e della Visione, Sezione di Fisiologia, Universita' di Verona, Strada Le Grazie 8, 37134 Verona, Italy, mario.buffelli@univr.it

Robert W. Burgess The Jackson Laboratory, 600 Main St., Bar Harbor, ME 04609, USA, rburgess@jax.org

Franklin A. Carrero-Martínez Department of Biology, University of Puerto Rico, Mayagüez, Mayagüez, Puerto Rico 00681-9012, franklin.carrero@upr.edu

Akira Chiba Department of Biology, University of Miami, 234 Cox Science Center, 1301 Memorial Drive, Coral Gables, FL 33124, USA, akira.chiba@miami.edu

Alexander A. Chubykin The Picower Institute for Learning and Memory, Massachusetts Institute of Technology, 77 Massachusetts Avenue, 46-3301, Cambridge, MA 02139, USA, chubykin@mit.edu

James C. Clemens Department of Biochemistry, Purdue University, 175 S. University St., West Lafayette, IN 47907, USA, jclemens@purdue.edu

Staffan Cullheim Department of Neuroscience, Karolinska Institutet, SE-171 77 Stockholm, Sweden, staffan.cullheim@ki.se

Michael A. Fox Department of Anatomy and Neurobiology, Virginia Commonwealth University Medical Campus, Box 980709, Richmond, VA 23298-0709, USA, mafox@vcu.edu

Juan Mauricio Garré Dominick P Purpura Department of Neuroscience, Albert Einstein College of Medicine, 1410 Pelham Parkway South, Room 704, Bronx, NY 10804, USA

Andrew M. Garrett Department of Biology, Graduate Program in Neuroscience, The University of Iowa, Iowa City, IA 52242, USA

Tanja Angela Godenschwege Department of Biological Sciences, Florida Atlantic University, Sanson Science Building 1/209, 777 Glades Road, Boca Raton, FL 33431, USA, tanjag@biology.fau.edu

Y. Kate Hong Program in Neuroscience, Harvard Medical School, Boston MA, 02115, USA; Department of Molecular and Cellular Biology, Harvard University, Fairchild Bldg, 7 Divinity Ave., Cambridge, MA 02138, USA, yhong@fas.harvard.edu

Michael Hortsch Department of Cell and Developmental Biology, University of Michigan, BSRB, 109 Zina Pitcher Place, Ann Arbor, MI 48109, USA, hortsch@umich.edu

Hitesh Kathuria Department of Biochemistry, Purdue University, 175 S. University St., West Lafayette, IN 47907, USA

Lars V. Kristiansen Research Laboratory for Stereology and Neuroscience, H. S. Bispebjerg University Hospital, Copenhagen, Denmark, lkri0062@bbh.regionh.dk

Catherine E. Krull Biologic and Materials Sciences, University of Michigan, 5211 Dental, 1011 N. University Ave., Ann Arbor, MI 48109-1078, USA, krullc@umich.edu

Daniel J. Liebl Miller School of Medicine, University of Miami, Miami Project to Cure Paralysis, P.O. Box 016960 R-48, Miami, FL 33101, USA, dliebl@miami.edu

Devi Majumdar Department of Biological Sciences, Vanderbilt Kennedy Center for Research on Human Development, Vanderbilt University, 465 21st Avenue South, Nashville, TN 37232, USA

Hisakazu Ogita Division of Molecular and Cellular Biology, Department of Biochemistry and Molecular Biology, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017 Japan

Sylwia Owczarek Protein Laboratory, Department of Neuroscience and Pharmacology, University of Copenhagen, Faculty Of Health Sciences, Blegdamsvej 3B, DK-2200 Copenhagen, Denmark

Suzanne Paradis Department of Biology, Brandeis University, P.O. Box 549110, Waltham, MA 02454-9110, USA, paradis@brandeis.edu

Bibiana Scelfo Dipartimento di Neuroscienze – Sezione di Fisiologia, Istituto Nazionale di Neuroscienze, Universita' di Torino, Corso Raffaello 30, 10125 Torino, Italy

Dietmar Schreiner Department of Biology, The University of Iowa, Iowa City, IA 52242, USA

Kang Shen Department of Biological Sciences, Stanford University, 371 Serra Mall, Gilbert 109, Stanford, CA 94305-5020, USA, kangshen@stanford.edu

Yoshimi Takai Division of Molecular and Cellular Biology, Department of Biochemistry and Molecular Biology, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017 Japan, ytakai@med.kobe-u.ac.jp

Sebastian Thams Department of Neuroscience, Karolinska Institutet, SE-171 77 Stockholm, Sweden, sebastian.thams@ki.se

Hideru Togashi Division of Molecular and Cellular Biology, Department of Biochemistry and Molecular Biology, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017 Japan

Hisashi Umemori Molecular and Behavioral Neuroscience Institute, University of Michigan, BSRB, 109 Zina Pitcher Place, Ann Arbor, MI 48109, USA, umemoh@umich.edu

Smitha Babu Uthaman Department of Biological Sciences, Florida Atlantic University, Sanson Science Building 1/209, 777 Glades Road, Boca Raton, FL 33431, USA

Philip Y. Wang Laboratory of Neurochemistry, National Institute on Deafness and Other Communication Disorders, National Institutes of Health, Bethesda, MD 20892, USA; Department of Biology, College of Chemical and Life Sciences and Neuroscience and Cognitive Science Program, University of Maryland, College Park, MD 20742, USA

Donna J. Webb Department of Biological Sciences and Vanderbilt Kennedy Center for Research on Human Development, Vanderbilt University, VU station B, Box 35-1634, Nashville, TN 37235, USA, donna.webb@vanderbilt.edu

Joshua A. Weiner Department of Biology, Graduate Program in Neuroscience, The University of Iowa, Iowa City, IA 52242, USA, joshua-weiner@uiowa.edu

Robert J. Wenthold Laboratory of Neurochemistry, National Institute on Deafness and Other Communication Disorders, National Institutes of Health, Bethesda, MD 20892, USA, wenthold@nidcd.nih.gov

Peter S. Walmod Protein Laboratory, Department of Neuroscience and Pharmacology, Faculty of Health Sciences, University of Copenhagen, Blegdamsvej 3B, DK-2200 Copenhagen, Denmark, psw@sund.ku.dk

Masahito Yamagata Department of Molecular and Cellular Biology, Harvard University, Fairchild Bldg, 7 Divinity Ave., Cambridge, MA 02138, USA, yamagatm@mcb.harvard.edu

Masahiro Yasuda Molecular and Behavioral Neuroscience Institute, University of Michigan, BSRB, 109 Zina Pitcher Place, Ann Arbor, MI 48109, USA

Chapter 1
A Short History of the Synapse – Golgi Versus Ramón y Cajal

Michael Hortsch

The history of the synapse started not only as a struggle between two ideas but also as a feud between the two founding fathers of modern neuroscience, the Italian Camillo Golgi (1843–1926) and the Spaniard Santiago Ramón y Cajal (1851–1934). Preceding their groundbreaking portrayals of the nervous system structure, Robert Remak (1815–1865), Theodore Schwann (1810–1882), Otto Friedrich Karl Deiters (1834–1863), and others had published only rudimentary histological descriptions of nerves and of some other parts of the nervous system. However, the limited resolution of the microscopic analysis at that time did not allow them to elucidate the cellular details and the functional relationships between individual nervous system components. In 1872, Joseph von Gerlach (1820–1896) formulated the first theory to explain the cellular organization of the nervous system (Gerlach 1872). His model, the Reticular Theory, postulated that the nervous system consists of a continuous syncytial network or reticulum. Nerve fibers, dendrites, and neuronal cells would be directly connected to each other by cytoplasmic bridges with the neuronal cell bodies providing only nourishment support.[1] Over the following years, Joseph von Gerlach together with Camillo Golgi became the major proponents of the initially widely accepted Reticular Theory. Ironically, it was a fortuitous discovery by Camillo Golgi that ultimately led to its demise.

[1] J. Gerlach J (1872) Von dem Rückenmark. In: Stricker S (eds) Handbuch der Lehre von den Geweben des Menschen und der Thiere. Verlag von Wilhelm Engelmann, Leipzig on page 684: ". . .the finest divisions of the protoplasmic processes take part in the formation of the fine nerve fiber network, which I consider to be an essential constituent of the gray matter of the spinal cord. . . .(T)he neuronal and cytoplasmic extensions of the cells in the gray matter are therefore connected in two ways with the nerve fibers of the spinal cord. First, by means of the nerve process. . .and secondly through the finest branches of the protoplasmic processes, which become a part of the fine nerve fiber net of the gray matter."

M. Hortsch (✉)
Department of Cell and Development Biology, University of Michigan,
Ann Arbor, MI 48109-2200, USA
e-mail: hortsch@umich.edu

M. Hortsch, H. Umemori (eds.), *The Sticky Synapse*,
DOI 10.1007/978-0-387-92708-4_1, © Springer Science+Business Media, LLC 2009

In 1873, Camillo Golgi reported a novel histological staining procedure, which selectively highlights a small number of neuronal cells at random while leaving most other neurons unstained (Golgi 1873). This effect is achieved by impregnating fixed neuronal tissues with potassium dichromate and silver nitrate. All stained cells are entirely filled with a brown or black precipitate of silver chromate, revealing even slender dendritic and axonal processes. In 1887, Santiago Ramón y Cajal learned about this novel histological method and developed it further to reveal even minute details of neuronal structures (Fig. 1.1). Over the following years, both Ramón y Cajal and Golgi used this staining technique for a detailed survey of many neuronal tissues. From his results, Santiago Ramón y Cajal concluded that the nervous system is not a continuous network, but rather consists of separate, discontinuous units or cells.

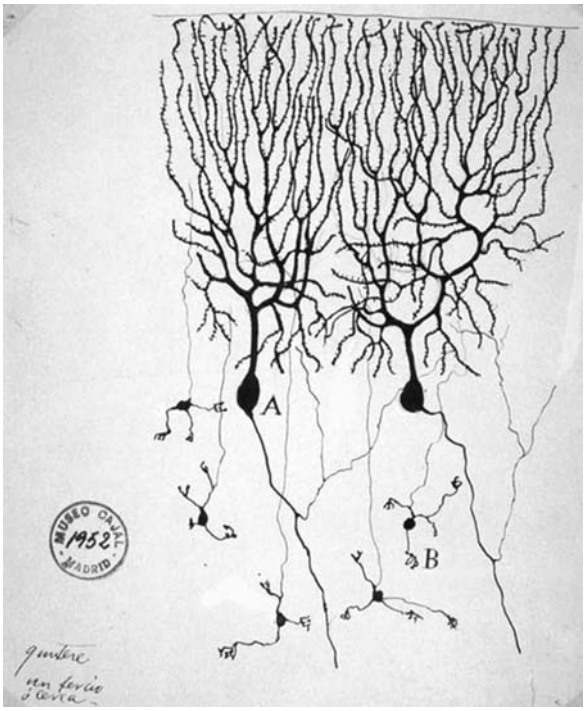


Fig. 1.1 Drawing of Purkinje (**A**) and granule cells (**B**) from an adult pigeon cerebellum by Santiago Ramón y Cajal (Golgi method), 1899. Instituto Santiago Ramón y Cajal, Madrid, Spain

Feeling scientifically isolated at his position as professor of histology and pathological anatomy in Barcelona, Ramón y Cajal traveled to the October 1889 meeting of the German Anatomical Society, which was held at the University of Berlin (Ramón y Cajal 1937). There he made the acquaintance of Rudolph Albert von Kölliker (1817–1905), Wilhelm His (1831–1904), Heinrich Wilhelm Gottfried von Waldeyer-Hartz (1836–1921), Arthur van Gehuchten (1861–1914), and other eminent histologists. After viewing Ramón y Cajal's

preparations, Albert von Kölliker in particular encouraged him to publish his findings more widely and later even confirmed and extended them with his own work.

Based on Santiago Ramón y Cajal's conclusions and the results of other researchers, Wilhelm von Waldeyer-Hartz in 1891 published a paper, in which he outlined an alternative theory, the Neuron Doctrine of the nervous system (Waldeyer-Hartz 1891), which subsequently received overwhelming support throughout the scientific community. In his publication, von Waldeyer-Hartz used for the first time the term "neuron" (Greek "νευρων" for sinew or tendon) to describe the separate cellular subunit that is common to all neuronal tissues. At that time, it had become clear that most neuronal cells consist of three different subcellular domains: the neuronal cell body or soma, fine tree-like cytoplasmic processes, and a single long fiber-like extension. Inspired by their branch-like structure and after the Greek word "δεντρο" for tree, Wilhelm His in 1889 had suggested the use of the phrase "dendrites" for the finer cytoplasmic neuronal processes (His 1889). Later in 1896, Albert von Kölliker added the term "axon" (Greek "αξον" for axle or axis) for the long, fiber-like extension (von Koelliker 1896). Over the following years, Santiago Ramón y Cajal in Spain and Arthur van Gehuchten in Belgium independently modified and extended the Neuron Doctrine by adding the Law of Dynamic Polarization, which states that neuronal signals only travel in one direction in a neuron, from dendrites and cell bodies to axons (Berlucchi 1999).

However, as the acceptance of the Neuron Doctrine grew, it raised a new problem. Neither von Waldeyer-Hartz's hypothesis nor Ramón y Cajal's morphological analysis offered an explanation of how a neuronal signal would be transferred from one neuronal cell to the next. Although specialized contact regions between neurons were soon suspected to be responsible for this process, no mechanistic explanation would be forthcoming for a considerable time. When preparing the 6th edition of his *Handbook of Human Physiology*, Sir Michael Foster (1836–1907) secured the assistance of his student Sir Charles Scott Sherrington (1857–1952) for writing the chapter on the Central Nervous System (Foster and Sherrington 1897). They both felt that a proper term for describing these special contact points between neurons was lacking and requested the help of Arthur Woolgar Verrall (1851–1912), a classical Greek scholar at the Trinity College in Cambridge (Tansey 1997). Verrall suggested the term "synapse" from the Greek "συν" (syn meaning together) and "απτειν" (haptein meaning to clasp), which was adapted by Foster and Sherrington and thereby introduced as the scientific term for describing neuronal contacts.

In 1906, the accomplishments of Camillo Golgi and Santiago Ramón y Cajal were jointly recognized with the Nobel Prize for Physiology or Medicine, the first of many to honor discoveries in the field of neuroscience (Table 1.1). The committee awarded the prize to both scientists "in recognition of their work on the structure of the nervous system" (Grant 2007). In his acceptance speech, given December 12, 1906, in Stockholm, Santiago Ramón y Cajal summarized his extensive histological work and that of other scientists, which argued against

Table 1.1 Nobel Prizes for Physiology or Medicine, which have been awarded for basic neuroscience discoveries

1906	Camillo Golgi and Santiago Ramón y Cajal "in recognition of their work on the structure of the nervous system"
1932	Sir Charles Sherrington and Lord Edgar Douglas Adrian "for their discoveries regarding the functions of neurons"
1936	Sir Henry Halett Dale and Otto Loewi "for their discoveries relating to chemical transmission of nerve impulses"
1944	Joseph Erlanger and Herbert Spencer Gasser "for their discoveries relating to the highly differentiated functions of single nerve fibers"
1957	Daniel Bovet "for his discoveries relating to synthetic compounds that inhibit the action of certain body substances, and especially their action on the vascular system and the skeletal muscles"
1961	Georg von Békésy "for his discoveries of the physical mechanism of stimulation within the cochlea"
1963	Sir John Eccles, Alan Lloyd Hodgkin, and Andrew Fielding Huxley "for their discoveries concerning the ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane"
1967	Ragnit Granit, Haldan Keffer Hartline, and George Wald "for their discoveries concerning the primary physiological and chemical visual processes in the eye"
1970	Sir Bernard Katz, Ulf von Euler, and Julius Axelrod "for their discoveries concerning the humoral transmittors in the nerve terminals and the mechanism for their storage, release, and inactivation"
1977	Roger Guillemin and Andrew Viktor Schally "for their discoveries concerning the peptide hormone production of the brain" and Rosalyn Yalow for "for the development of radioimmunoassays of peptide hormones"
1981	Roger W. Sperry "for his discoveries concerning the functional specialization of the cerebral hemispheres" and David H. Hubel and Torsten N. Wiesel "for their discoveries concerning information processing in the visual system"
1986	Stanley Cohen and Rita Levi-Montalcini "for their discoveries of growth factors"
1991	Erwin Neher and Bert Sakmann "for their discoveries concerning the function of single ion channels in cells"
1997	Stanley B. Prusiner "for his discovery of Prions – a new biological principle of infection"
2000	Arvid Carlsson, Paul Greengard, and Eric R. Kandel "for their discoveries concerning signal transduction in the nervous system"
2004	Richard Axel and Linda B. Buck "for their discoveries of odorant receptors and the organization of the olfactory system"

the Reticular Theory and in support of the Neuron Doctrine[2] (Ramón y Cajal 1967). He acknowledged that in the future, novel techniques might reveal new structures and mechanisms and how neuronal cells are connected. However,

[2] S. Ramón y Cajal, Nobel Prize Lecture (1967): "From the whole of these facts, the neuronal doctrine of His and of Forel, accepted by many neurologists and physiologists, is derived as an inevitable postulate... The irresistible suggestion of the reticular conception, of which I have spoken to you has led several physiologists and zoologists to object to the doctrine of the propagation of nerve currents by contact or at a distance. All their allegations are based on the findings by incomplete methods showing far less than those which have served to build the imposing edifice of the neuronal conception."

from the data, which were available to him, he rejected a continuous neuronal network and therefore the Reticular Theory. Much to his chagrin, Camillo Golgi in his Nobel lecture, which he had delivered the previous day, presented a diametric opposite view and a scathing rejection of the Neuron Doctrine[3] (Golgi 1967). In his autobiography, Santiago Ramón y Cajal describes Camillo Golgi's Nobel lecture as self-serving and his attitude as arrogant (Ramón y Cajal 1937). He accuses him of ignoring the experimental results of other researchers and of "worship of his own ego."[4] Certainly no love was lost between these two pioneers of neuroscience. Until his death in 1926, Camillo Golgi remained an ardent supporter of the Reticular Theory.

First insights into the mechanism and the chemical nature of synaptic signals came at the beginning of the 20th century, mainly from the laboratory of John Newport Langley (1852–1925) at Cambridge University in England. In 1904, his student Thomas Renton Elliott (1877–1961) discovered that adrenaline from the adrenal gland mimics the effect of sympathetic nerve innervation on various muscles and glands (Elliott 1905). Adrenaline had previously been recognized as a small bioactive molecule derived from the adrenal medulla; its structure had been determined and it had just been chemically synthesized. Although he mistakenly assumed that adrenaline, rather than noradrenaline, might be released from the peripheral sympathetic nerve endings, Thomas Elliott laid the conceptual foundation for the activity of neurotransmitters as small chemical molecules that bridge the synaptic gap between nerve endings and their targets (Elliott 1904). The identification of the first genuine neurotransmitter can be credited to another former student of Langley, Sir Henry Halett Dale (1865–1968) (Tansey 2006). Together with his colleague Arthur James Ewins (1882–1957) at the Wellcome Physiological Research Laboratories he identified and isolated acetylcholine from a bacterial contamination of the cereal fungus ergot and characterized its physiological activity (Dale 1914, Ewins 1914). However, the final proof of its physiological significance fell to his friend and 1936 fellow Nobel laureate (Table 1.1), the physiologist Otto Loewi (1873–1961). Otto Loewi's experiments on explanted frog hearts established that signaling across most synapses is mediated by small chemical compounds, now referred to as neurotransmitters (Loewi 1921). Nevertheless, it took a considerable time until it was generally accepted that synaptic signal transduction usually is based on a chemical and not on a bioelectrical mechanism. Even in 1937, Sir John Eccles (1903–1997), one of the 1963 Nobel laureates

[3] C. Golgi, Nobel Prize Lecture (1967): "I shall ... confine myself to saying that, while I admire the brilliancy of the (neuron) doctrine, which is a worthy product of the high intellect of my illustrious Spanish colleague, I cannot agree with him on some points of an anatomical nature."

[4] S. Ramón y Cajal, Recollections of My Life (1937): "Contrary to what we all expected, instead of pointing out the valuable facts, which he (Golgi) had discovered, he attempted in it to refloat his almost forgotten theory of interstitial nerve nets. Likewise he considered it unnecessary to correct any of his old theoretical errors, or of his lapses of observation."

for his work on the ionic mechanisms of nerve cell excitation and inhibition (Table 1.1), still favored an electrical transmission model (Eccles 1937). Only later he converted to Henry Dale's view of a chemical-centered signal transmission at synapses. Over the next decades, a number of additional neurotransmitters were identified. For example, a student of Henry Dale, Ulf Svante von Euler (1905–1983), demonstrated in 1946 that noradrenalin is the major neurotransmitter of the sympathetic nervous system (von Euler 1946). Also the first mechanistic details about the process of synaptic transmission began to emerge. At the beginning of the 1950s, Sir Bernard Katz (1911–2003) and his coworkers showed that neurotransmitter molecules were released from the presynaptic termini in discrete quantal amounts (Fatt and Katz 1952, Del Castillo and Katz 1954), and Julius Axelrod (1912–2004) and his research group demonstrated that secreted neurotransmitters were not just rapidly degraded by enzymes, but also taken up and recycled by the surrounding cells (Whitby et al. 1961). In 1961, their contributions to the understanding of synaptic processes were also recognized by the Nobel Prize committee (Table 1.1).

Although physiological and biochemical experiments settled the chemical nature of synaptic signal transmission, a new microscopic technique was needed to elucidate the fine structure of synaptic organization and to demonstrate how transmitters are released into the synaptic cleft. In 1933, Ernst August Friedrich Ruska (1906–1988) had developed the first electron microscope, and at the beginning of the 1950s, this technology was used to investigate the subcellular organization of many biological tissues including neuronal cells. These initial studies by Eduardo de Robertis (1913–1988), J. David Robertson (1922–1995), Fritiof S. Sjöstrand (born 1912), and others provided the final morphological proof for the central hypothesis of the Neuron Doctrine, the existence of a discontinuity or gap between the pre- and the postsynaptic cell (Robertson 1953, Estable, Reissig and De Robertis 1954, Sjöstrand 1958). The superior magnification and resolution of the electron microscope also revealed additional structural details, which had not been seen using other techniques. One such revelation was the presence of small secretory vesicles in the presynaptic terminus (De Robertis and Bennett 1955, Palay 1956). These membrane vesicles were soon postulated to contain neurotransmitters and thus provided an explanation for the quantal release of neurotransmitters, which had been observed by Sir Bernard Katz and his group. Early electron microscopic analyses also reported an electron-dense region at the membrane of the postsynaptic neuron, now referred to as the postsynaptic density (Akert et al. 1969). Despite this wealth of new structural information about the general subcellular organization of synaptic connections, electron microscopic studies alone were unable to identify the molecular components and proteins that form them.

Over the last 40 years, genetic, biochemical, molecular biological and genomic approaches have finally revealed a plethora of protein components, which constitute the synaptic apparatus. Among these synaptic proteins are components of the secretory pathway, which are responsible for vesicle transport, polypeptides involved in membrane vesicle docking and fusion, neurotransmitter receptors

and ion channels, enzymes responsible for neurotransmitter processing, inactivation and uptake, cytoskeletal elements and scaffolding proteins, extracellular matrix components, cellular signaling proteins, and also cell adhesion molecules (CAMs). As synapses are special contact points between neurons and their targets it may not be surprising that CAMs are important components of synaptic connections. However, it was somewhat unexpected that many CAMs, which have been found at synapses, also have important non-synaptic functions in neuronal cell and in tissues outside the nervous system, such as during neuronal differentiation, axonal pathfinding, cell migration, or epithelial stability. Only relatively few adhesive molecules appear to have an exclusive synaptic function. Several general characteristics of CAMs appear to be of special relevance for their functional role at synapses. Synaptic contacts contain not only homophilic CAMs but also heterophilic CAMs, which interact with a heterologous binding partner on the pre- or postsynaptic cell surface. Such heterophilic pairs of adhesive molecules or pre- versus postsynaptic differences in the expression of CAM-interacting proteins might play a role in the differential organization of pre- and postsynaptic membranes. Besides their extracellular adhesive specificities, many CAMs also exhibit evolutionarily well-conserved, cytoplasmic binding activities to different cytoskeletal elements. These interactions appear to be of special importance in integrating different structural and functional aspects of the synaptic apparatus. More recently, it has become increasingly clear that many adhesive proteins directly or indirectly influence various cellular signaling processes. This is relevant not only during synapse formation but also during synaptic functioning and remodeling. In turn, cellular signaling processes, especially those involving protein phosphorylation and proteolysis as well as interactions with the cytoskeleton are known to regulate the adhesive ability of many CAMs. For synaptic CAMs, this may be important for facilitating synaptic plasticity, when existing synaptic connections are weakened or severed. Therefore, synaptic CAMs may be directly involved in processes like long-term potentiation and depression and synaptic remodeling. Almost all of the major CAM families have one or more representatives that are expressed at synaptic contacts, and different classes of synapses appear to have specific subsets of adhesive proteins. Although all chemical synapses share some general characteristics, this variety of CAMs is certainly part of the structural and functional diversity between different types of synaptic contacts. While our knowledge of how different CAM families contribute to synapse formation and functioning is still incomplete, the available data support some general themes, which are summarized above and in the following chapters. In the coming years, our understanding of the crucial role of CAMs at synapses will certainly deepen and possibly new adhesive molecules will join the list of known synaptic CAMs that are discussed in this book.

Today the term synapse is used in connection with three different types of cellular junctions (Yamada and Nelson 2007). It describes contact points not only between neuronal cells but also between immune cells and epithelial cells. An immunological synapse is the interface between antigen-presenting cells

(e.g., macrophages, dendritic or activated B cells) and lymphocytes (Grakoui et al. 1999). Adhesion complexes, such as tight and adherent junctions, between epithelial cells are sometimes referred to as epithelial synapses (Yamada and Nelson 2007). However, usually the term synapse alludes to neuronal synapses. The majority of neuronal synapses are chemical based, as presumed in the preceding part of this chapter. More recently, evidence for an alternative type of neuronal synapse has emerged, which uses an electrical mode of signal transduction. These electrical synapses are formed by connexin/pannexin-containing gap junctions, which allow the direct propagation of the action potential from one neuronal cell to the next without the need for a chemical transmitter intermediate (Connors and Long 2004). As gap junctions form small cytoplasmic connections between neighboring cells, the existence of electrical synapses might be viewed as a partial exoneration of Camillo Golgi's old idea that neuronal cells are directly linked to each other. The relative importance of electrical versus chemical synapses currently remains unclear. Obviously, the structural and functional interactions between neuronal cells and their targets have grown increasingly intricate and multifaceted. As Santiago Ramón y Cajal pointed out in 1906 "Unfortunately, nature seems unaware of our intellectual need for convenience and unity, and very often takes delight in complication and diversity. Besides, we believe that we have no reason for scepticism. While awaiting the work of the future, let us be calm and confident in the future of our work" (Ramón y Cajal 1967).

References

Akert K, Moor H, Pfenninger K et al. (1969) Contributions of new impregnation methods and freeze etching to the problems of synaptic fine structure. In: Akert K and Waser PG (eds) Prog Brain Res. Elsevier Publishing Company, Amsterdam/London/New York

Berlucchi G (1999) Some aspects of the history of the law of dynamic polarization of the neuron. From William James to Sherrington, from Cajal and van Gehuchten to Golgi. J Hist Neurosci 8:191–201

Connors BW and Long MA (2004) Electrical synapses in the mammalian brain. Annu Rev Neurosci 27:393–418

Dale HH (1914) The action of certain esters and ethers of choline. J Pharmacol 6:147–190

De Robertis ED and Bennett HS (1955) Some features of the submicroscopic morphology of synapses in frog and earthworm. J Biophys Biochem Cytol 1:47–58

Del Castillo J and Katz B (1954) Quantal components of the end-plate potential. J Physiol 124:560–573

Eccles JC (1937) Synaptic and neuro-muscular transmission. Physiol Rev 17:538–555

Elliott TR (1904) On the action of adrenalin. J Physiol 31(suppl.):XX–XXI

Elliott TR (1905) The action of adrenalin. J Physiol 32:401–467

Estable C, Reissig M and De Robertis E (1954) Microscopic and submicroscopic structure of the synapsis in the ventral ganglion of the acoustic nerve. Exp Cell Res 6:255–262

Ewins AJ (1914) Acetylcholine, a new active principle of ergot. Biochem J 8:44–49

Fatt P and Katz B (1952) Spontaneous subthreshold activity at motor nerve endings. J Physiol 117:109–128

Foster M and Sherrington CS (1897) A Text Book of Physiology. Macmillan and Co., New York
Gerlach J (1872) Von dem Rückenmark. In: Stricker S (eds) Handbuch der Lehre von den Geweben des Menschen und der Thiere. Verlag von Wilhelm Engelmann, Leipzig
Golgi C (1873) Suella struttura della sostanza grigia del cervello [On the structure of the brain grey matter]. Gazzetta Medica Italiana Lombarda 33:244–246
Golgi C (1967) The Neuron Doctrine – Theory and Facts (Lecture delivered Decmber 11, 1906). In: (eds) Nobel Lectures, Physiology or Medicine 1901–1921. Elsevier Publishing Company, Amsterdam-London-New York
Grakoui A, Bromley SK, Sumen C et al. (1999) The immunological synapse: a molecular machine controlling T cell activation. Science 285:221–227
Grant G (2007) How the 1906 Nobel Prize in Physiology or Medicine was shared between Golgi and Cajal. Brain Res Rev 55:490–498
His W (1889) Die Neuroblasten und deren Entstehung im Embryonalen Mark. Abhandlungen der mathematisch-physischen Classe der Königl. Sächsischen Gesellschaft der Wissenschaften 15:311–372
Loewi O (1921) Über humorale Übertragbarkeit der Herznervenwirkung. I. Mitteilung. Pflüger's Arch ges Physiol 189:239–242
Palay SL (1956) Synapses in the central nervous system. J Biophys Biochem Cytol 2:193–202
Ramón y Cajal S (1937) Recollections of my Life. M.I.T. Press, Cambridge, MA
Ramón y Cajal S (1967) The structure and connexions of neurons (Lecture delivered December 12, 1906). In: (eds) Nobel Lectures, Physiology or Medicine 1901–1921. Elsevier Publishing Company, Amsterdam-London-New York
Robertson JD (1953) Ultrastructure of two invertebrate synapses. Proc Soc Exp Biol Med 82:219–223
Sjöstrand FS (1958) Ultrastructure of retinal rod synapses of the guinea pig eye as revealed by three-dimensional reconstructions from serial sections. J Ultrastruct Res 2:122–170
Tansey EM (1997) Not committing barbarisms: Sherrington and the synapse, 1897. Brain Res Bull 44:211–212
Tansey EM (2006) Henry Dale and the discovery of acetylcholine. C R Biol 329:419–425
von Euler US (1946) A specific sympathomimetric ergone in adrenergic nerve fibres (Sympathin) and its relations to adrenaline and nor-adrenaline. Acta Physiol Scand 12:73–97
von Koelliker A (1896) Handbuch der Gewebelehre des Menschen. Engelmann, Leipzig
Waldeyer-Hartz W (1891) Ueber einige neuere Forschungen im Gebiete der Anatomie des Centralnervensystems. Deutsche medicinische Wochenschrift 17:1213–1218, 1244–1216, 1287–1219, 1331–1212 and 1350–1216
Whitby LG, Axelrod J and Weil-Malherbe H (1961) The fate of H^3-norepinephrine in animals. J Pharmacol Exp Ther 132:193–201
Yamada S and Nelson WJ (2007) Synapses: sites of cell recognition, adhesion, and functional specification. Annu Rev Biochem 76:267–294