

COLD SPRING HARBOR SYMPOSIA ON QUANTITATIVE BIOLOGY

VOLUME XL

The Synapse

COLD SPRING HARBOR LABORATORY

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**COLD SPRING HARBOR SYMPOSIA
ON QUANTITATIVE BIOLOGY
VOLUME XL**

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COLD SPRING HARBOR SYMPOSIA ON QUANTITATIVE BIOLOGY

VOLUME XL

*COLD SPRING HARBOR SYMPOSIA
ON QUANTITATIVE BIOLOGY*

Founded in 1933

by

REGINALD G. HARRIS

Director of the Biological Laboratory

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Volume XXXIII (1968) Replication of DNA in Microorganisms
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Level
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Foreword

The way we perceive bits of information, often to memorize and later to think with, has long proved a major challenge to the scientific mind. In attacking this problem we assume that no paradox exists in using our brains to tell us what they are and how they function. Instead we largely worry whether we have yet evolved into a life-form intelligent enough to probe the myriad levels of complexity that underly even the simplest forms of rational behavior.

The fundamental units we must study are the nerve cells and the synapses that link them together. In doing so, we must understand how electrical impulses are transmitted along neurons as well as work on the factors that determine how, when and where the synaptic interconnections are made. By now many of the questions surrounding the nerve impulse itself have been resolved. But the question of what synapses are and how they are made remains a mystery which currently is intriguing to an increasingly large number of the world's better scientists.

The time thus seemed right to choose the synapse as the focus for our 40th Symposium. Helping to arrange the program were Drs. Seymour Benzer, Eric Kandel, Stephen Kuffler, John Nicholls, David Potter and Gunther Stent. Their combined list of suggested speakers revealed such a great diversity of interests and emphasis that decisions regarding the final program at times seemed somewhat capricious. The end result, however, was a most exciting meeting attended by over two hundred and forty people. Most pleasantly, many of our guests commented that it was the best gathering of neurobiologists that has occurred in their memories.

Vital to this success were the well-coordinated efforts of Helen Parker and her staff, who handled all the organizational aspects. Equally impressive, they inspired our cook to produce meals unlike any seen in the recent history of our Symposia.

Support for this meeting, in particular in the form of travel funds for our speakers from abroad, came from the National Science Foundation, the National Institutes of Health, and the U.S. Energy and Research Development Administration. Their continued support for so many years is most greatly appreciated.

This resulting Symposium volume was edited with dispatch by Ms. Nancy Ford, ably assisted by Ms. Annette Zaninovic and Mr. Stephen Jarowski. To persuade some sixty speakers to produce readable manuscripts within a finite time is never a simple task, and we are most fortunate in possessing an editorial staff that compares well with those of the most skilled commercial publishers.

J. D. Watson

Contents

Symposium Participants	v
Foreword	xvii

STRUCTURAL ASPECTS OF SYNAPTIC FUNCTION

A Guide to the Synaptic Analysis of the Neuropil	<i>S. L. Palay and V. Chan-Palay</i>	1
Preservation of Synaptic Structure by Rapid Freezing	<i>J. E. Heuser, T. S. Reese and D. M. D. Landis</i>	17
Stimulation-induced Depletion of Vesicles, Fatigue of Transmission and Recovery Processes at a Vertebrate Central Synapse	<i>M. V. L. Bennett, P. G. Model and S. M. Highstein</i>	25
The Structure and Permeability of Isolated Hepatocyte Gap Junctions	<i>D. A. Goodenough</i>	37
The Protein Components of the Gap Junction	<i>J. R. Duguid and J. P. Revel</i>	45
Permeable Junctions	<i>W. R. Loewenstein</i>	49

CHEMISTRY OF SYNAPTIC TRANSMISSION

Recent Studies on the Comparative Biochemistry of the Cholinergic Neuron	<i>M. J. Dowdall, G. Fox, K. Wachtler, V. P. Whittaker and H. Zimmermann</i>	65
Axonal Transport of Vesicles Carrying [³ H]Serotonin in the Metacerebral Neuron of <i>Aplysia californica</i>	<i>J. H. Schwartz, J. E. Goldman, R. T. Ambron and D. J. Goldberg</i>	83
Differential Labeling of Glial Cells and GABA-inhibitory Interneurons and Nerve Terminals following the Microinjection of [β - ³ H]Alanine, [³ H]-DABA and [³ H]GABA into Single Folia on the Cerebellum	<i>J. S. Kelly and F. Dick</i>	93
Modulation of Transmitter Release by Calcium Ions and Nerve Impulses	<i>R. Rahamimoff, S. D. Erulkar, E. Alnaes, H. Meiri, S. Rotshenker and H. Rahamimoff</i>	107
β -Bungarotoxin, a Phospholipase That Stimulates Transmitter Release	<i>R. B. Kelly, S. G. Oberg, P. N. Strong and G. M. Wagner</i>	117
Octopamine Neurons in Lobsters: Location, Morphology, Release of Octopamine and Possible Physiological Role	<i>E. A. Kravitz, P. D. Evans, B. R. Talamo, B. G. Wallace and B. A. Battelle</i>	127
Substance P and Excitatory Transmitter of Primary Sensory Neurons	<i>M. Otsuka and S. Konishi</i>	135
Electrogenic Effects of Neutral Amino Acids on Neurons of <i>Aplysia californica</i>	<i>J. S. Kehoe</i>	145
Cyclic Nucleotides, Protein Phosphorylation and Synaptic Function	<i>K. G. Beam and P. Greengard</i>	157

THE ACETYLCHOLINE RECEPTORS

Molecular Basis for Postjunctional Conductance Increases Induced by Acetylcholine C. F. Stevens	169
The Number of Acetylcholine Molecules in a Quantum and the Interaction between Quanta at the Subsynaptic Membrane of the Skeletal Neuromuscular Synapse H. C. Hartzell, S. W. Kuffler and D. Yoshikami	175
Analysis of Cooperativity of Drug-Receptor Interaction by Quantitative Iontophoresis at Frog Motor End Plates K. Peper, F. Dreyer and K. D. Müller	187
Characterization of <i>Torpedo californica</i> Acetylcholine Receptor: Its Subunit Composition and Ligand-binding Properties M. A. Raftery, R. L. Vandlen, K. L. Reed and T. Lee	193
Facets of the Structures of Acetylcholine Receptors from <i>Electrophorus</i> and <i>Torpedo</i> A. Karlin, C. L. Weill, M. G. McNamee and R. Valderrama	203
Some Structural Properties of the Cholinergic Receptor Protein in Its Membrane Environment Relevant to Its Function as a Pharmacological Receptor J.-P. Changeux, L. Benedetti, J.-P. Bourgeois, A. Brisson, J. Cartaud, P. Devaux, H. Grünhagen, M. Moreau, J.-L. Popot, A. Sobel and M. Weber	211
On the Interaction between Cobra α -Neurotoxin and the Acetylcholine Receptor A. Maelicke and E. Reich	231
Turnover of Acetylcholine Receptors in Skeletal Muscle P. N. Devreotes and D. M. Fambrough	237
The Biochemical Properties and Regulation of Acetylcholine Receptors in Normal and Denervated Muscle J. P. Brookes, D. K. Berg and Z. W. Hall	253
Control of ACh Sensitivity in Rat Muscle Fibers T. Lomo and R. H. Westgaard	263
Persistence of Junctional Acetylcholine Receptors following Denervation E. Frank, K. Gautvik and H. Sommerschild	275
Synaptic Organization and Acetylcholine Sensitivity of Multiply Innervated Autonomic Ganglion Cells S. Roper, D. Purves and U. J. McMahan	283

GATING CURRENTS IN NERVE

Properties of the Sodium Channel Gating Current F. Bezanilla and C. M. Armstrong	297
Gating Mechanism for the Activation of the Sodium Conductance in Nerve Membranes E. Rojas	305

GENETIC AND DEVELOPMENTAL APPROACHES

Anatomy and Development of Identified Cells in Isogenic Organisms F. Levinthal, E. Macagno and C. Levinthal	321
Synaptic Specificity in the Cerebellar Cortex: Study of Anomalous Circuits Induced by Single Gene Mutations in Mice P. Rakic	333

FORMATION AND MAINTENANCE OF SYNAPSES

Enrichment of Nerve-Muscle Synapses in Spinal Cord-Muscle Cultures and Identification of Relative Peaks of ACh Sensitivity at Sites of Transmitter Release G. D. Fischbach, D. K. Berg, S. A. Cohen and E. Frank	347
Central Nervous System Synapses in Cell Culture P. G. Nelson	359
Synapse Formation and Neurotrophic Effects on Muscle Cell Lines Y. Kido-koro, S. Heinemann, D. Schubert, B. L. Brandt and F. G. Klier	373
Biochemical Studies on the Development of Primary Sympathetic Neurons in Cell Culture P. H. Patterson, L. F. Reichardt and L. L. Y. Chun	389
Physiological and Morphological Studies on Developing Sympathetic Neurons	

in Dissociated Cell Culture <i>P. H. O'Laque, P. R. MacLeish, C. A. Nurse, P. Claude, E. J. Furshpan and D. D. Potter</i>	399
The Formation of Neuromuscular Synapses <i>M. R. Bennett and A. G. Pettigrew</i>	409
Formation and Elimination of Synapses in Skeletal Muscles of Rat <i>J. K. S. Jansen, D. C. Van Essen and M. C. Brown</i>	425
Physiological Properties of Nerve-Muscle Junctions Developing In Vivo <i>M. J. Dennis and C. A. Ort</i>	435
Cell Junctions in Development, with Particular Reference to the Neural Tube <i>J.-P. Revel and S. S. Brown</i>	443

LONG-TERM CHANGES AND SPECIFICITY OF CONNECTIONS

Responses of Spinal Motor Neurons to Section and Restoration of Peripheral Motor Connections <i>M. Kuno</i>	457
A Common Presynaptic Locus for the Synaptic Changes Underlying Short-term Habituation and Sensitization of the Gill-withdrawal Reflex in <i>Aplysia</i> <i>E. R. Kandel, M. Brunelli, J. Byrne and V. Castellucci</i>	465
Modification and Regeneration of Synaptic Connections in Cultured Leech Ganglia <i>S. Miyazaki, J. G. Nicholls and B. G. Wallace</i>	483
Repair of Specific Neuronal Pathways in the Leech <i>D. Van Essen and J. K. S. Jansen</i>	495
Topographic Polarity of the Optic Tectum Studied by Reimplantation of the Tectal Tissue in Adult Goldfish <i>M. G. Yoon</i>	503

RETINA AND VISUAL SYSTEM

Ultrastructural Analysis of Functional Changes in the Synaptic Endings of Turtle Cone Cells <i>S. F. Schaeffer and E. Raviola</i>	521
Transmission of Signals from Photoreceptors of Ganglion Cells in the Eye of the Turtle <i>D. A. Baylor and R. Fettiplace</i>	529
Synaptic Transmission from Photoreceptors to Bipolar and Horizontal Cells in the Carp Retina <i>A. Kaneko and H. Shimazaki</i>	537
Receptor Coupling in the Toad Retina <i>G. L. Fain, G. H. Gold and J. E. Dowling</i>	547
Signal Transmission from Photoreceptors to Ganglion Cells in the Visual System of the Giant Barnacle <i>S. Ozawa, S. Hagiwara, K. Nicolaysen and A. E. Stuart</i>	563
Synaptic Chemistry of Identified Cells in the Vertebrate Retina <i>D. M. K. Lam</i>	571
Functional Architecture of Area 17 in Normal and Monocularly Deprived Macaque Monkeys <i>D. H. Hubel, T. N. Wiesel and S. LeVay</i>	581
The Functional Organization of Projections from Striate to Prestriate Visual Cortex in the Rhesus Monkey <i>S. M. Zeki</i>	591
Synaptic Competition in the Kitten's Visual Cortex <i>C. Blakemore, R. C. Van Sluyters and J. A. Movshon</i>	601
Adaptive Synaptic Connections Formed in the Visual Pathways in Response to Congenitally Aberrant Inputs <i>R. W. Guillery and V. A. Casagrande</i>	611

MODEL SYSTEMS

Basilar Membrane Motion <i>G. Zweig</i>	619
Nonlinear Interactions Underlying Visual Orientation Behavior of the Fly <i>T. Poggio and W. Reichardt</i>	635
Analyzing Natural Images: A Computational Theory of Texture Vision <i>D. Marr</i>	647
Peripheral Feedback in the Leech Swimming Rhythm <i>W. B. Kristan, Jr. and G. S. Stent</i>	663

Summary	
The Synapse	C. F. Stevens 675
Name Index	681
Subject Index	691

A Guide to the Synaptic Analysis of the Neuropil

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So far as our present knowledge goes we are led to think that the tip of a twig of the [axonal] arborescence is not continuous with but merely in contact with the substance of the dendrite or cell body on which it impinges. Such a special connection of one nerve cell with another might be called a *synapsis*.

(p. 929)

... each *synapsis* offers an opportunity for a change in the character of nervous impulses, that the impulse as it passes over from the terminal arborescence of an axon into the dendrite of another cell, starts in that dendrite an impulse having characters different from its own.

(p. 969)

—Foster and Sherrington (1897)

The criteria for recognizing synapses in morphological preparations arise directly out of the definitions that Sherrington (Foster and Sherrington 1897) gave when he introduced this term.¹ By extracting the essence from the two passages introducing this article, we can reconstruct the definition in the following way: a synapse is a special connection of one nerve cell with another, a site where the nerve impulse passes over from the terminal of an axon into another cell and starts in that cell an impulse having characters different from its own. Or, as Eccles paraphrased it in 1964, a synapse is an area "of close contact ... specialized for effective transmission from one neurone to another." Thus from the beginning, the concept of the synapse had both morphological and functional components. On the morphological side, the concept requires an intercellular gap, a specific location and a special cellular apparatus for the transfer of the nerve impulse from one cell to another. Sherrington was aware of the contemporary histological observations made with the Golgi method, especially those by Ramón y Cajal, who was his guest on the occasion of the 1894 Croonian Lecture. As early as 1888, Ramón y Cajal had seen the terminations of axons in Golgi preparations of the central nervous system, most convincingly in the cerebellar cortex, where he recognized the terminals of the basket fibers around the bases of Purkinje cells and the rosettes by means of which the mossy fibers articulate with the dendrites of granule cells. But a distinctive terminal apparatus was not

recognized until 1897, the same year as Sherrington's first use of the word *synapse*, when Held, and later Auerbach (1898), described specialized structures—called end feet by Held—at the terminations of axons impinging upon cell bodies and dendrites. These end feet, or boutons, were small, spherical or bulbous swellings at the tips of fibers or even in their course, and these were filled with mitochondria, which were readily stained by acid fuchsin. The end feet provided the locus of specialized apparatus on the *presynaptic* side of the connection. The postsynaptic site was early identified by Ramón y Cajal (1894) and other morphologists as the perikaryon or dendritic shaft without necessarily any postsynaptic specialization. Although the numerous and varied dendritic appendages were suspected of having some specific postsynaptic role, their significance, and indeed their reality, was debated for many years. The Sherringtonian insight that the transferred impulse starts a new impulse with its own characters in the postsynaptic partner failed to stir morphologists of the time into finding a counterpart in the form of the dendrite.

THE FINE STRUCTURE OF SYNAPSES

The criteria for recognizing a synapse at the light microscopic level of inspection therefore included first, a junction between an axon and a nerve cell body or its processes and second, some sign of specialization at the junction parallel to the local functional differentiation—a change in shape of the axon (a varicosity, swelling, rosette or terminal bud), an accumulation of mitochondria or a definite termination. Identification at the electron microscopic level (Palay 1956a,b; Peters et al. 1976) requires at least the same criteria, which are easy to satisfy, and adds several further distinctions visible only at this level of inspection. These include first, the definition of the junction itself; second, new structural specializations within the presynaptic element; third, structural specializations within the postsynaptic element; and fourth, the discovery of totally unexpected dendro-dendritic and axo-axonic synapses. The greatly increased number of structural features disclosed by the electron microscope permits the construction of a vastly increased number of distinctive patterns. As a result, it is now possible in some parts of the central nervous system not only to identify synapses, but also to recognize the specific synapses made by particular neuronal types (see, for example, Palay and Chan-Palay 1974). This new capability opens the possibility of mapping the

¹Fulton (1949) records in a footnote that the term *synapse* was suggested to Sherrington's co-author, Michael Foster, by a Greek scholar at Cambridge named Verrall. The original *synapsis* (from *συναπτω* — clasp) was apparently modified into *synapse* very early (perhaps by way of the plural for *synapsis*, *synapses*) since Sherrington uses the modern form in his Silliman Lectures of 1904 (published in 1906).



Figure 1. The synaptic interface of an axo-dendritic synapse in the dentate nucleus of a monkey, *Macaca mulatta*: sv, synaptic vesicles; sc, synaptic cleft; psd, postsynaptic density; sd, secondary postsynaptic densities. A coated vesicle is visible on the postsynaptic side near the bottom of the field. Magnification, 252,000 \times .

organization of the central nervous system with a high degree of detail. The delineation of the detailed structure and functional patterns of synapses in defined parts of the central nervous system is now a major preoccupation of neurocytologists.

Figure 1 provides an example of the essential structural specializations revealed by electron microscopy of synaptic junctions. The simplest components are an axonal terminal containing clusters of small vesicles, a dendrite with dense material adherent to the cytoplasmic side of its membrane, and a synaptic cleft distinctly separating the apposed surface membranes of the two partners. The presynaptic mitochondria expected from light microscopic preparations are better shown in lower power micrographs (Fig. 2).

The Synaptic Cleft

Each cell in the central nervous system, as elsewhere in the organism, is enclosed in an independent cell membrane and is separated from its neighbors by a continuous interstitial space. Although the dimensions of this space vary widely according to location and the methods of preparing the tissue, it is generally about 20–30 nm deep. It probably contains glycoproteins, which may be either attached to or an integral part of the adjacent plasmalemmas (Pease and Peterson 1972). In most electron micrographs prepared by the present conventional methods, this interstitial material is very imperfectly preserved (or at least poorly demonstrated) and only appears as occasional patches of threadlike material crossing the interstitial space.

The synaptic cleft is that part of the continuous interstitial space which intervenes between the two members of the synapse and across which the nerve impulse must somehow “pass over” (Palay 1956b). It, too, varies widely in depth, but the deviations from the average range of the general interstitial space bear a consistent relation to the type of synapse involved (see below). In Figure 1, the synaptic cleft is 2–3 times as deep as the nonsynaptic interspace and contains a dense lamina of poorly defined texture, thought to be largely glycoprotein (Pease and Peterson 1972; Cotman and Taylor 1974). This lamina approximates in extent the widened zone of the junction and the dense material adherent to the cytoplasmic side of the postsynaptic plasmalemma. The critical point to notice is that the apposed plasmalemmas are intact, discrete and independent. Before the application of electron microscopy to the study of the nervous system, the synaptic cleft could not be visualized, and the nature of the effective junction between nerve cells was reasoned to be a disjunction. In some favorable specimens with large synaptic junctions, the interface between the two members appeared in the light microscope as a dense, but tenuous, membrane or plate, to which Bodian (1942) gave the name *synaptolemma*. Electron microscopy shows this to be a cleft continuous with the normal interstitial space and bounded by apposed plasmalemmas (Palay 1956a,b).

The Pre- and Postsynaptic Densities

Although the plasmalemmas on either side of the synaptic cleft were originally described (Palay 1956a,b) as “thickened” and the use of this misleading expression still persists, it is clear that the plasmalemmas themselves are not morphologically altered as they pass through the region of the synapse (Fig. 1). Instead, dense material attaches to their cytoplasmic surfaces. This material is usually described as filamentous in texture, although individual filaments are not often discernible because of overlap in the thickness of the sections. Instead, the material has a shaggy, free margin in the cytoplasmic matrix. Cotman and his