efficient as its homologs apoE3 or E2, so that mainte-
nance or outgrowth of neurites is impaired. Thirdly, it is
notable that the typical clinical treatments of AD, mostly
aimed at compensating the decline in neurotransmitters
such as acetylcholine, are not even touched upon. Other
promising leads such as the inflammation hypothesis,
which holds that local inflammation processes in the
brain cause the abnormal reactions and degeneration
of neurons (review, E. McGeer and P. McGeer, Curr.
Pharm. Des. *5*, 821–836, 1999), or the oxidation hypothe-
sis, which traces neuronal damage back to accumulat-
ing oxidative stress (review, C. Behl, Prog. Neurobiol.
57, 301–323, 1999), are also not discussed.

Who should buy the book? I am not sure. The articles
represent an excellent summary of molecular and cell
biological approaches to the Alzheimer problem, focus-
ing mainly on APP and presenilin biology, with many
useful references to earlier key papers. The book was
up to date when it appeared (1998), but given the rapid
progress in the field, it is now already substantially out
of date. It does not contain several major recent findings,
such as: (a) the identification of β-secretases that belong
to the family of membrane-bound aspartic proteases
(Vassar et al., Science *286*, 735–741, 1999; Sinha et al.,
Nature *402*, 537–540, 1999; Yan et al., Nature *402*, 533–
537, 1999; Hussain et al., Mol. Cell. Neurosci. *14*, 419–
427, 1999); (b) the suggestion that PS-1 may itself be
an aspartic protease that is responsible for its own pro-
teolytic processing and for the γ-secretase activity
cleaving APP (Wolfe et al., Nature *398*, 513–517, 1999);
(c) the observation that immunization with Aβ can reduce
the amyloid burden in the brain, which opens an unex-
pected avenue to treatment (Schenk et al., Nature *400*,
173–177, 1999); (d) the discovery of mutations in the *Tau*
gene that cause a family of frontotemporal dementias
with parkinsonism linked to chromosome 17 (FTDP-17;
Poorkaj et al., Ann. Neurol. *43*, 815–825, 1998; Clark et
al., Proc. Natl. Acad. Sci. USA *95*, 13103–13107, 1998;
Spillantini et al., Proc. Natl. Acad. Sci. USA *95*, 7737–
7741); (e) the strong correlation between neurofibrillary
pathology in AD and an activated form of the protein
kinase cdk5 (Patrick et al., Nature *402*, 615–622, 1999;
Alvarez et al., FEBS Lett. *459*, 421–426, 1999), to name
a few. Therefore, if I wanted to get an overview of the
field of APP and presenilin biology, I would consult one
of the recent reviews that continue to appear within
regular scientific journals (e.g., de Strooper and König,
Nature *402*, 471–472, 1999; Haass and de Strooper, Sci-
ence *286*, 916–919, 1999; Selkoe, Nature *399*, A23–A31,
1999; Hardy and Gwinn-Hardy, Mol. Med. Today *5*, 514–
517, 1999). Moreover, books like this one are not avail-
able on the internet. Reading habits are changing, and
articles that cannot be downloaded on the computer
will fade into oblivion quickly, no matter how scholarly
they are. Instead other means of communication will
take over and provide up-to-date information, including
reviews in regular journals with online access, all electronic
journals (e.g., Alzheimer Disease Reviews, www.coa.uky.
edu/ADReview), or the digest of the latest research results
on special web pages (e.g., www.alzforum.org).

Eckhard Mandelkow
Max-Planck-Unit for Structural Molecular Biology
Hamburg, Germany

The Fruitfly Neuromuscular Junction Flexes Its Muscle

Neuromuscular Junctions in Drosophila
Edited by Vivian Budnik and L. Sian Gramates
San Diego, CA: Academic Press (1999). 289 pp. $59.95

Neuromuscular junctions (NMJs) of many species have
often paved the way to important discoveries because
of their large size and accessibility for experimental ma-
nipulation. During the past decade, the popularity of
fruitfly NMJs has sharply risen because elegant electro-
physiological techniques have been combined with very
sophisticated genetic and molecular tools to provide
key insights into the development and function of the
NMJ. The recent release of the entire sequence of the
fly genome will greatly accelerate research in this field
and probably attract more biologists to study these syn-
apses. Hence, the timing of this useful compendium on
NMJs in *Drosophila* is quite appropriate.

Neuromuscular Junctions in Drosophila aims at pro-
viding the reader with a basic introduction to many ad-
vances made using NMJs in *Drosophila*. The 11 chap-
ters, each written by different authors, focus either on
developmental aspects or on physiological/functional
aspects. Most chapters provide short and informative
summaries covering the literature through the beginning
of 1998. Each chapter is only about 20 pages long,
allowing for a quick read but not a comprehensive cover-
age of individual topics. The study of NMJs can logically
be divided into three main areas: motor neurons, mus-
cles, and the interplay between the two.

Motor neurons arise in the ventral portion of each
embryonic hemisegment and target a specific muscle
of the body wall. The axonal pathways of the motor
neurons converge when they exit the CNS, and each
axon takes a highly predictable path to reach a specific
muscle. The targeting efficiency in wild-type embryos
is almost 100%. The whole process takes about 3 hr
and has been extensively studied at the molecular level,
revealing that numerous attractive and repulsive se-
creted proteins and their receptors control the pathways
traveled by the axons and their targeting to the muscles.
Although axon pathfinding has been studied in great
detail, target recognition and presynaptic terminal dif-
ferentiation have been much less well characterized
(Chiba, chapter 1). Interestingly, most larval motor neu-
rons, unlike most tissues, survive metamorphosis. They
appear to be structurally respecified to reinnervate adult
muscles. Much of the remodeling occurs in the thorax
where there is first a withdrawal of the larval synapses,
followed by the elaboration of adult specific synapses.
Hence, the process of adult NMJ formation is very differ-
ent from that observed in embryos (see below) where
motor neurons arrive at an already formed array of mus-
cle fibers (Fernandes and Keshishian, chapter 10).

Muscle development in fruitfly embryos has been
studied quite extensively. Unlike vertebrate muscles,
which consist of bundles of myotubes, *Drosophila* mus-
cles consist of single myotubes that form through fusion
of several myoblasts. Each muscle or myotube has a
distinctive shape, size, and attachment site. One would

expect that myoblasts are selected in groups that fuse to form a particular myotube. However, expression data suggest that a single myoblast (a founder) is first specified, and that other nearby myoblasts are then recruited to fuse with the founder myoblast. When myoblast fusion fails, each founder will develop into a small mono-nucleate myotube that is properly innervated. The other myoblasts remain rounded and are not innervated. Hence the 30 founders per hemisegment gate the process of muscle differentiation in the embryo (Bate et al., chapter 2). Adult founder cells have not yet been identified. Indeed, much less is known about adult muscle development, and what we know seems to indicate that different muscles may use different developmental strategies (Fernandes and Keshishian, chapter 10).

Synaptogenesis, or the formation of the synapse after target recognition, has been described in morphological and electrophysiological terms such as clustering of neurotransmitter receptors, electrical properties of the muscles, and channel activity, but it remains a largely unexplored field at the molecular level. In *Drosophila*, the fast neurotransmitter at the NMJs is L-glutamate. The glutamate receptors that permit the influx of Na^+ are present in the muscles prior to synapse formation and cluster upon contact of the growth cones between 14 and 20 hr of development. However, most and possibly all the electrical properties of muscles develop independently of neural input. The localization of transmitter receptors in the muscles and the localization of the active zone (where synaptic vesicles are released) on the other hand depend on neuromuscular interactions. Hence, the basic elements assemble independently pre- and postsynaptically but they localize only in response to signals from their partner (Broadie, chapter 3).

Upon contacting the muscles, three types of boutons are formed. Type I are large and use glutamate as primary neurotransmitter. Type II terminals are derived from only two neurons per hemisegment; they are small, and predominantly use octopamine as neurotransmitter. Type III terminals are only present on specific muscles and contain mainly large dense core vesicles. Type II and III have not been associated with an electrical response from the muscles, although they do contain the same type of vesicles as type I boutons. Boutons cannot easily be observed in most embryos as they only mature after the growth cone has contacted the muscle (13–16 hr) and the filopodia have retracted and formed varicosities (16–17 hr). The development of type I boutons leads to the maturation of the subsynaptic reticulum (SSR) in the muscle, whereas type II boutons form structures that look more like hemidesmosomes (Rheuben et al., chapter 4).

The subcellular localization of numerous proteins within each bouton is highly orchestrated, and the Discs Large (DLG) protein seems to play a preponderant role in clustering synaptic proteins. DLG is a MAGUK (membrane-associated guanylate kinase) essential for the clustering and targeting of Shaker channels at type I boutons. For this, DLG relies on the ability of some of its PDZ domains to interact with the carboxy-terminal domain of the channels. Similarly, DLG binds to and is required for the localization of Fasciclin II, a protein that is related to a vertebrate neural cell adhesion molecule and which is required for the maintenance and plasticity

of fruitfly NMJs. DLG may also play a role in clustering glutamate receptors but other PDZ-containing proteins may be involved as well. The network of proteins that plays an important role in clustering and targeting proteins pre- and postsynaptically, and their impact on synaptic maintenance and structural plasticity will remain an intense area of research in the coming years (Gramates and Budnik, chapter 5).

Fruitfly NMJs allow the study of signal transduction pathways that mediate synaptic plasticity. Indeed, many learning and memory mutants affect cAMP metabolism as well as the electrophysiological properties of, and short term plasticity at the NMJs. An interesting neuro-modulatory pathway has been discovered through electrophysiological studies of the larval NMJ. This pathway is regulated by a PACAP-like peptide (Pituitary adenylyl cyclase-activating polypeptide 38) that is probably secreted from type I boutons upon high-frequency stimulation. Binding of the peptide to its receptor activates the Ras pathway as well as proteins in the cAMP pathway. The end result is a delayed enhancement of the voltage-gated potassium channels; its physiological significance is unknown (Hannan and Zhong, chapter 6).

By combining genetic manipulations, electron microscopy, FM1–43 dye uptake experiments, confocal laser microscopy, and electrophysiological studies at embryonic or third instar larval NMJs, significant progress has been made in understanding the molecular mechanisms of neurotransmitter release (Littleton et al., chapter 7) and endocytosis (Stimson and Ramaswami, chapter 8). Much of the work on neurotransmitter release is based on a reverse genetic approach, as numerous vertebrate proteins have previously been isolated and cloned on the basis of biochemical experiments. By cloning the *Drosophila* homologs and making targeted mutations, it has been possible to determine the consequences of alterations in specific proteins implicated in the process, thereby providing very valuable clues about their in vivo role (Littleton et al., chapter 7). One of the genes that was not isolated by a reverse genetic strategy is the *shibire* gene, which encodes the GTPase dynamin, an essential protein required for endocytosis in most cells. Temperature-sensitive mutations in this protein cause paralysis of adult flies and have allowed elegant in vivo manipulations, from which evidence has been gathered concerning the presence of different vesicle pools, the sites where endocytosis occurs, the time necessary to recycle vesicles, the intermediate structures, and the calcium dependence of the process (Stimson and Ramaswami, chapter 8).

Several potassium channel subunits were first cloned in *Drosophila* because mutations in channel subunits cause leg shaking when the flies are anesthetized with ether: e.g., *Shaker*, *ether-a-go-go*, and *Hyperkinetic*. At least four different types of potassium channels have been identified in embryonic, larval, and adult muscles. They include two voltage-activated potassium currents—one transient (I_A) and one delayed (I_K)—and two calcium-activated currents—a fast (I_{CF}) and a slow current (I_{CS}). Calcium channels have only been identified relatively recently, and these channels seem to correspond to the vertebrate L- or T-type channels (Singh and Wu, chapter 9).

The last two chapters cover the development of the

adult neuromuscular system (Fernandes and Keshi-shian, chapter 10) and networks controlling motor neuron activity in the adult (Trimarchi et al., chapter 11). They illustrate how relatively little we know about the adult fly when compared to the embryo and the third instar larvae. Many features of adult development seem to be different when compared to that of embryos, and the neuronal circuitry of the adult is quite complicated. However, I anticipate that studies of adult fly NMJs will become more and more popular as new electrophysiological preparations for NMJs are developed. The last chapter provides a nice springboard to the future as it illustrates how some of the more simple adult circuits can already be tackled.

For a novice, this book is very useful as it covers a lot of ground and is clearly written. For those working in the field it is a nice reference work. A more extensive coverage of many of the topics covered here should soon be considered.

Hugo J. Bellen
Howard Hughes Medical Institute
Departments of Molecular and Human Genetics,
   Cell and Molecular Biology, and Neuroscience
and Program in Developmental Biology
Baylor College of Medicine
Houston, Texas 77030

Information Released on the Synapse

*Neurotransmitter Release: Frontiers
in Molecular Biology*
Edited by Hugo Bellen
London: Oxford University Press (1999). 458 pp. $120.00

Information is transferred from one nerve cell to the next by regulated release of neurotransmitter. This normally occurs at specialized connections called synapses, where a complex molecular machinery is assembled to control sustained transmitter release. The discovery over 40 years ago that neurotransmitter is released in packets called quanta, together with the ultrastructural characterization of synapses, focused attention on synaptic vesicles as key organelles of neurotransmitter release. Synaptic vesicles are targeted to and cluster at special regions of the axon, where they undergo regulated fusion. Electrical signals arriving at the presynaptic terminal cause calcium influx, which in turn triggers a set of molecular events leading to the fusion of synaptic vesicles with the plasma membrane and the emptying of neurotransmitter into the synaptic cleft. In the last decade, significant advances have been made in understanding the molecular basis of transmitter release, and *Neurotransmitter Release: Frontiers in Molecular Biology* provides an up-to-date synthesis of facts and ideas on this subject.

A major part of current research in synaptic transmission is focused on understanding the series of protein–protein and protein–lipid interactions underlying the life cycle of the synaptic vesicle. Synaptic vesicles probably need to be docked to the active zone before they can fuse with the membrane. How vesicles recognize the active zone and remain docked there (and not elsewhere in the presynaptic plasma membrane) remains largely a mystery. Although there is evidence for the role of rab proteins and SNARE proteins in the docking step, neither class appears currently to have all the attributes of a molecular device mediating selective target recognition. Once docked, vesicles are thought to undergo maturation reactions, referred to as priming, before they become fusion competent. Then, an increase in intraterminal calcium leads to fusion of the vesicle with the plasma membrane—this step probably involves the SNARE proteins, but the exact nature of the reaction leading to fusion is unclear at present. Once exocytosis occurs, vesicular components are retrieved for reuse by clathrin-mediated, and perhaps other forms of endocytosis. The recycling machinery at the synapse no doubt has much in common with other cellular endocytic pathways. The key components of the endocytic machinery are being uncovered, but the exact signals for and mechanisms of endocytosis remain hidden.

A remarkable similarity of proteins involved in secretion in different cell types and across species has allowed the integration of data from different model systems and organisms. For example, homologs of many of the proteins that mediate secretion in yeast are involved in neurotransmitter release. Given the rapid growth of factual knowledge about membrane traffic in general, it is becoming increasingly difficult, though necessary, for a specialist to keep track of developments in such diverse fields as cell division in yeast and synapse formation in mouse. Therefore, *Neurotransmitter Release* provides a welcome compilation of the latest information on the molecular basis of synaptic vesicle traffic.

The book is well organized. It starts with an overview of the cell biology of the synapse, which is followed by a chapter reviewing key physiological techniques used to measure synaptic function. Oddly enough, this chapter on techniques does not consider the classical electrophysiological method of measuring postsynaptic current to assay vesicle exocytosis (this method, however, is invoked extensively in a later chapter describing the use of the squid giant synapse as a model system). Chapter 3 presents a comprehensive account of proteins involved in membrane trafficking at synapses, touching upon the history of identification of synaptic proteins and their characterization. This chapter also provides information about the structure of proteins involved in vesicle fusion, and detailed discussion of current ideas of how membrane fusion might occur. Chapter 4 describes the role of membrane phospholipids, particularly phosphoinositides, in signaling as well as regulation of protein function at the synapse. The chapter on neurotransmitter transporters at synapses is a veritable encyclopedia, and with its nearly 400 references will surely serve as a valuable resource. Neurotoxins have greatly aided the understanding of the role of specific proteins in neurotransmission, and chapter 6 describes the mechanism of action and targets of many of these toxins. The four subsequent chapters focus on specific model systems—first the squid giant synapse,