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Synaptic Structure and Function: Dynamic Organization Yields Architectural Precision

Review

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The power of the brain is based upon the extraordinary abilities of nerve cells to communicate with each other at specialized intercellular junctions called synapses. As other papers in this issue of *Cell* discuss (see Garrity and Zipursky, 1995; Keynes and Cook, 1995), other forms of interneuronal communication also occur, especially during neuronal development. Here we focus on the communication taking place at the most prominent type of synapse, the "chemical" synapse. At such synapses, signal transmission is mediated by neurotransmitters that are rapidly secreted, from the presynaptic neuron onto the postsynaptic neuron, in response to a presynaptic action potential. Synaptic transmission requires elaborate structural specializations in both presynaptic and postsynaptic cells, as well as precise spatial alignment between the structures on the two sides of the synapse. In addition, because transmission at synapses is highly modifiable, the architecture of synapses must also be very dynamic. This review is intended as a guide to the well-appreciated structural organization of chemical synapses and attempts to relate the structure of synapses to their function as sites of neuronal communication.

Essential Structures of Synapses

Each of the billions of synapses in a mammalian brain has the same general task: to release and detect neurotransmitters. Thus, although there is a broad spectrum of synapses, all share certain fundamental structural features that are responsible for conserved functions. We begin with a brief survey of these general architectural features. For a more comprehensive overview of this subject, see Heuser and Reese (1977).

Presynaptic Structure

The terminals of presynaptic neurons all need to synthesize and store neurotransmitters and then secrete these transmitters in a regulated manner. Except for rare examples of nonvesicular transmitter release (Attwell et al., 1993), neurotransmitters are stored within membrane-bound organelles called synaptic vesicles. A typical presynaptic terminal may contain a few hundred synaptic vesicles, though this number varies widely among synapses (Harris and Kater, 1994) and, as discussed below, changes dynamically while the synapse is active. Synaptic vesicle size varies, largely depending upon the type of neurotransmitter contained within the vesicles. Generally, vesicles containing fast-acting neurotransmitters are approximately 50 nm in diameter and appear to have clear centers when viewed with an electron microscope. A second class of synaptic vesicles, which contain slower-acting transmitters and proteinaceous material, are usually larger in diameter (up to several hundred nanometers) and have an electron-dense core.

Synaptic vesicles are not distributed uniformly within presynaptic cytoplasm; most congregate less than 0.5 μm away from the part of the presynaptic plasma membrane that abuts the postsynaptic neuron. These clusters of vesicles appear to be a mix of both newly formed and preexisting vesicles (Betz and Bewick, 1992; Ryan and Smith, 1995). Most vesicles within the cluster are linked to each other, to cytoskeletal elements within the terminal, or to both. This association probably helps to target vesicles to specific destinations and to keep them in place. It has been proposed that these links are composed of synapsin, a protein that associates with purified vesicles in a phosphorylation-sensitive manner (Landis et al., 1988; Hirokawa et al., 1989). Consistent with the idea that synapsin helps vesicle organization, it recently has been shown that perturbation of synapsin, by either antibody microinjection or genetic knockout, disperses the cluster of vesicles and causes diminished neurotransmitter release in response to high frequency stimulation (Rosahl et al., 1995; Pieribone et al., 1995). Thus, maintenance of the vesicle cluster seems to be essential for sustained synaptic function.

Because many nerve terminals secrete transmitters rapidly, it is expected that at least some synaptic vesicles are in a fusion-competent state (Kelly, 1993). A subset of vesicles within the cluster are found to be in contact with a specialized region of the presynaptic plasma membrane; these are defined as docked and are thought to include those that are ready for fusion (Schweizer et al., 1995). The proteins responsible for docking vesicles at the membrane are not yet clear, but may include the GTP-binding protein Rab3 as well as UNC-18 or SNARE proteins (or both) (Rothman, 1994; Schweizer et al., 1995; Scheller, 1995; Südhof, 1995).

Between the docked vesicles lies an electron-dense tangle of cytoskeletal elements and other structural proteins that may help organize the presynaptic cytoplasm (Landis et al., 1988; Hirokawa et al., 1989). The cytoskeleton of presynaptic terminals is not well understood, in part because conventional fixation methods do not preserve cytoskeletal elements as well as they preserve membrane-bound structures. One cytoskeletal element that has been identified near synaptic vesicles is a filamentous structure that has one of its ends attached to the plasma membrane. This protein appears to be fodrin, a brain-specific isoform of spectrin. Whatever the composition of these filaments, their polarized alignment seems ideal for delivering vesicles to the plasma membrane, although there is not yet any independent support for this idea. There are also reports of actin within the vesicle cluster (Hirokawa et al., 1989) and some evidence that actin and its motor protein, myosin, may influence the ability of vesicles to fuse (Bernstein and Bamburg, 1989; Mochida et al., 1994). Cytoplasm in the central region of the nerve terminal, away from the plasma membrane, contains few vesicles and is filled with linear arrays of microtubules and neurofilaments. These arrays are oriented along the long axis of the axon and appear to be continuous with the axonal cytoskeleton.

Presynaptic terminals release neurotransmitter from the docked synaptic vesicles via the process of calcium-regulated exocytosis (Katz, 1966; Heuser et al., 1979). Fusion of vesicles occurs in response to an action potential opening voltage-gated calcium channels in the presynaptic plasma membrane. These channels allow rapid influx of calcium into the presynaptic cytoplasm, and the resultant elevation of intracellular calcium concentration serves as a second messenger signal that triggers fusion. Since intracellular calcium concentration falls off steeply as a function of distance away from the calcium channels, the location of calcium channels relative to the fusion apparatus is critical and appears to vary among synapses (see below). A large array of proteins have been implicated in the process of vesicle fusion; these are reviewed elsewhere (Schweizer et al., 1995; Scheller, 1995; Südhof, 1995) and will not be discussed here.

Following vesicle fusion and release of neurotransmitter, the lipid and protein constituents of the vesicle transiently become part of the presynaptic plasma membrane and afterward are endocytosed for reuse. Although the precise mechanism of vesicle retrieval is not yet clear, clathrin-mediated endocytosis apparently is involved because plasma membrane pits and cytoplasmic vesicles coated with clathrin are most abundant within a few seconds after nerve terminals have secreted neurotransmitter (Heuser and Reese, 1973). It is widely thought that clathrin-coated pits constrict to form coated vesicles (Takei et al., 1995) and that these two structures represent sequential intermediates in a pathway for activity-dependent endocytic retrieval of vesicular membrane from the plasma membrane. The presynaptic cytoplasm also contains some endosome-like organelles, sometimes called cisternae. The amount of membrane within this compartment also increases following a bout of exocytosis, indicating that endosomes are another intermediate in synaptic vesicle retrieval (Heuser and Reese, 1973). Our understanding of the molecular processes responsible for sorting and removal of vesicle components from the endosome is limited (Kelly et al., 1993).

Presynaptic cytoplasm also contains mitochondria that are usually positioned some distance away from the synaptic vesicles. These organelles presumably are involved in energy metabolism and, perhaps, in regulation of intracellular calcium homeostasis. Some terminals also possess endoplasmic reticula that lie beneath the plasma membrane and are also thought to be involved calcium homeostasis (Henkart et al., 1976; Andrews and Reese, 1986).

Synaptic Cleft

The site of synaptic contact invariably includes a narrow space, between presynaptic and postsynaptic cells, called the synaptic cleft. The width of this cleft varies among synapses, but is typically about 50 nm. Although the size of the cleft determines how quickly secreted neurotransmitters reach the postsynaptic membrane, we know little about how this close separation is maintained. The synaptic cleft is filled with extracellular matrix, which contains a number of extracellular proteins thought to be important in synapse formation and stabilization, such as laminin and cell adhesion molecules (Hall and Sanes, 1993). At all synapses, there are invariably glial cells positioned near (or within) the synaptic cleft. These glia help remove neurotransmitters from the synaptic cleft and, in some cases, may play more active roles in interneuronal signaling.

Postsynaptic Structure

The postsynaptic cell has its own characteristic set of structural specializations that allow it to sense the presence of neurotransmitters secreted from the presynaptic cell. Most essential are neurotransmitter receptor proteins, which are highly concentrated at the portion of the postsynaptic membrane directly apposed to the presynaptic terminal. The extent of receptor clustering varies among synapses, perhaps regulating synaptic strength and speed. The region just beneath the receptor-laden postsynaptic membrane often has a characteristic protein-rich structure called the postsynaptic density. Many components of the density remain to be characterized, but it is known that it contains cytoskeletal proteins and other structural elements responsible for receptor clustering. The postsynaptic density may also contain molecules, such as protein kinases, that are responsible for altering the postsynaptic sensitivity to transmitters.

Most postsynaptic membranes exhibit a folded, nonplanar shape. Typically, the postsynaptic membrane is extended to form protuberances known as spines or invaginated to form postjunctional folds. It is thought that the increased surface area produced by these structures may maximize the numbers of postsynaptic receptors exposed to secreted transmitters. They may also modify the electrical signals produced by receptor activation and could compartmentalize signals produced by second messenger molecules, such as calcium (Harris and Kater, 1994; Martin, 1994). Within these structures are cytoskeletal elements that presumably maintain the shape of the structures. Endoplasmic reticula are commonly seen; these may help remove calcium ions, release them, or both. Some synapses also have vesicles within their postsynaptic regions. The functions of these vesicles are not clear, but they may be involved in trafficking of receptors and other membrane proteins.

Postsynaptic neurons are also capable of communicating with their presynaptic partners. This communication can occur via the exocytotic release of neurotransmitters (at so-called reciprocal synapses) or via nonexocytotic secretion of membrane-permeant signaling molecules. We regrettably must avoid discussing these topics in the interest of brevity.

Structural Specializations of Synapses

The previous section documents a set of structural features that characterize all synapses. However, the diversity of functions subserved by neurons also requires structural specializations that optimize particular synapses for different forms of synaptic transmission. Here we briefly consider these specializations by surveying the divergent structures of four types of synapses with different functions.

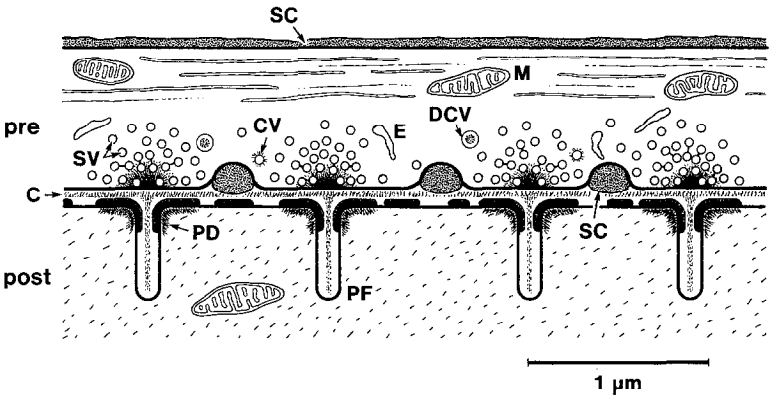

Figure 1. Schematic Structure of a Frog Neuromuscular Synapse

The presynaptic component of the active zone includes cytoplasm filled with small, clear-cored synaptic vesicles (SV), dense-cored synaptic vesicles (DCV), and numerous other organelles, including coated vesicles (CV), endosomes (E) and mitochondria (M). The presynaptic cell is enveloped by a Schwann cell (SC). The postsynaptic component of the active zone is characterized by postjunctional folds (PF) that appear thickened at their crests because of a high density of acetylcholine receptors and the postsynaptic density (PD). These two structures are separated by a narrow synaptic cleft (C).

The Peripheral Neuromuscular Junction

The best-studied example of a chemical synapse is one formed between motor neurons and muscle cells in the peripheral nervous system. This synapse is specialized to provide transient, fail-safe excitation of the postsynaptic muscle cell, ensuring muscle contraction whenever the motor neuron is active. As part of this assignment, the neuromuscular synapse is optimized for very rapidly releasing large quantities of acetylcholine, the excitatory neurotransmitter. The neuromuscular synapse of the frog has received the most attention (Katz, 1966) and, thus, will serve as our example of a strong, fast synapse. A more comprehensive overview of the organization of the neuromuscular synapse can be found in Hall and Sanes (1993).

A neuromuscular synapse consists of a highly branched presynaptic termination of the motor neuron that innervates a long, cylindrical muscle cell. At the level of the electron microscope, it can be seen that this single synapse consists of several hundred repeating structures, the active zones (Figure 1). Active zones are the subcellular sites of synaptic transmission. In the presynaptic terminal, an active zone can be identified by its large cluster of perhaps 1000 small, clear-cored synaptic vesicles that contain acetylcholine. In addition, these presynaptic terminals also contain a few larger, dense-cored vesicles that are thought to contain peptide transmitters that modulate synaptic transmission. The contents of these two different types of vesicles can be differentially secreted (Matteoli et al., 1988), indicating some differences in the mechanisms used to trigger their exocytosis.

The small synaptic vesicles dock by forming two rows on either side of the presynaptic density (Couteaux and Pecot-Dechavassine, 1970). There are 30–50 such vesicles lined up at each active zone. Normally, an action potential causes only one of these vesicles to fuse with the plasma membrane at each active zone, although all of these vesicles can fuse if the presynaptic action potential is sufficiently long (Katz and Miledi, 1979). It is not yet clear why such a small fraction of the docked vesicles are released; probably part of the answer is that only a fraction of the presynaptic calcium channels are opened during a single action potential (Llinas et al., 1981). In addition, not all docked vesicles may be fully competent to undergo fusion. Nonetheless, because there are hundreds of active zones in each presynaptic terminal, discharge of one vesicle's contents per active zone is adequate to ensure suprathreshold excitation of the postsynaptic muscle cell.

It is thought that voltage-gated calcium channels are in very close proximity to the docked vesicles, forming rows that may be within a few tens of nanometers of the rows of docked synaptic vesicles (Robitaille et al., 1990). The close proximity guarantees a rapid rise in calcium concentration at the vesicle fusion sites and allows exocytosis to follow presynaptic excitation in less than 1 ms. In this terminal, the coupling between calcium channels and exocytosis is so tight that opening of a single calcium channel appears sufficient to trigger vesicle fusion (Yoshikami et al., 1989).

The most remarkable structural feature of the postsynaptic area of a muscle cell is the tremendous accumulation of acetylcholine receptors. These receptors are heteromultimeric protein complexes whose structure and function are well known (Hall, 1992). The density of these receptors approaches 10,000 per square millimeter within the active zone, a packing density so high that these receptors must be the primary protein in this part of the postsynaptic membrane. Only a fraction of these receptors are activated during the release of acetylcholine from a single vesicle; because there are so many receptors, the resulting electrical response is quite large (approximately 5000 ion channels opened) and rather constant in amplitude (Fatt and Katz, 1952).

Acetylcholine receptors are not uniformly distributed on the postsynaptic membrane; instead, they appear to cluster selectively at the peaks of the folds in the postsynaptic membrane. This arrangement allows the receptors to detect quickly and efficiently the secretion of the contents of a single synaptic vesicle. The valleys of the postjunctional folds are thought to enable more rapid diffusion of acetylcholine away from the receptors, facilitating hydrolysis by acetylcholinesterase found in the synaptic cleft (Hall, 1992). These valleys also contain voltage-gated sodium channels that may boost the electrical signal produced by synaptic activity (Martin, 1994). The mechanisms of receptor clustering are not well understood, but likely involve a glycoprotein complex of 43 kDa protein, dystrophin, dystroglycans, agrin, and syntrophin (Sealock and

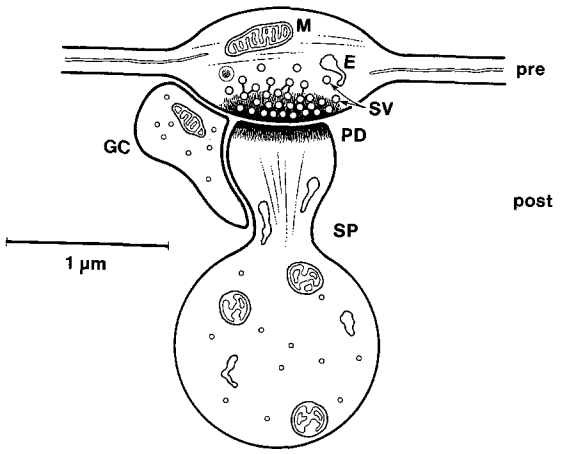

Figure 2. Schematic Structure of a PF Synapse in the Mammalian CNS

The presynaptic terminal is shaped into a bouton structure and is filled with synaptic vesicles (SV), mitochondria (M), and endosomes (E). The postsynaptic Purkinje cell makes contact with this bouton at a dendritic spine (SP), with its characteristic postsynaptic density (PD). A glial cell (GC) nestles between the two cells near their site of contact.

Froehner, 1994). A number of other proteins also colocalize with the receptors (Hall and Sanes, 1993) and may help form or maintain receptor clusters.

Fast-Acting Synapses within the Central Nervous System

Our second example of synaptic organization comes from among the great multitude of synapses in the mammalian central nervous system (CNS). Although we will generalize from observations of a number of CNS synapses, when possible we will focus on the so-called parallel fiber (PF) excitatory synapse between granule cells and Purkinje cells in the cerebellar cortex (Figure 2). A single Purkinje cell possesses more than 100,000 PF synapses; this is an extreme number for a CNS neuron, but the structure of this synapse still looks much like that of most other excitatory and inhibitory synapses within the CNS.

The PF synapse seems to be optimized for rapidly releasing small quantities of its neurotransmitter, glutamate, from a given presynaptic terminal and for generating small postsynaptic electrical responses. The glutamate released from the PF excites the postsynaptic Purkinje cell, producing a minute electrical current several orders of magnitude smaller than the postsynaptic current produced at the neuromuscular synapse. To excite the Purkinje cell sufficiently to produce an action potential, many such PF inputs must sum together (Barbour, 1993; Eilers et al., 1995).

The structure of the PF synapse nicely reflects its functional requirements. The presynaptic terminal of the PF synapse, like that of many other central synapses, consists of boutons, small spherical swellings of the presynaptic axon. A PF bouton has a diameter of 1–2 μm, and the opposing postsynaptic structure, the dendritic spine, is comparable in dimensions. Thus, these structures are much smaller in volume than their neuromuscular counterparts. While the presynaptic terminal of the PF synapse contains active zones, each terminal possesses only one to three active zones rather than the hundreds found at a neuromuscular synapse. Further, each presynaptic terminal contains a smaller complement of synaptic vesicles, typically 100–200 per active zone. A typical CNS bouton might have up to 50 docked vesicles, arranged in a grid-like array, unlike the linear rows of docked vesicles seen at the neuromuscular synapse (Akert, 1973). It is not yet clear what advantages come with such an arrangement. Despite this substantial number of docked vesicles, an action potential is likely to trigger the fusion of no more than one synaptic vesicle from a PF bouton (Barbour, 1993). This echoes observations at other CNS synapses, suggesting that many boutons release virtually no transmitter at all (Stevens, 1994).

One possible source of the low release probability of CNS synapses may be the presynaptic voltage-gated calcium channels. While the number and position of these channels are not yet known, there are suggestions that these terminals contain so few channels that sometimes an action potential opens none of them (Frenguelli and Malinow, Soc. Neurosci., abstract). Further, unlike the case at the neuromuscular synapse, calcium entering from more than one type of calcium channel seems necessary for optimum release of transmitter at CNS synapses (Takahashi and Momiyama, 1993; Wheeler et al., 1994; Mintz et al., 1995).

Postsynaptic structures may also contribute to the low efficacy of most CNS synapses. Unlike the large synaptic surface area of the neuromuscular junction, PF terminals contact the Purkinje cell dendrite at spines that are approximately 1 μm long and a fraction of 1 μm in diameter. While it has been proposed that these tiny spines attenuate current flow from the synapse to the main dendrites of the Purkinje cell, this notion has been largely discounted (Harris and Stevens, 1988). Instead, it is now thought that spines can act as local biochemical compartments by restricting the movement of intracellular messengers, such as calcium (Lisman and Harris, 1993).

The density of postsynaptic receptors seems to be another major cause of the low efficacy characteristic of most CNS synapses. While neurotransmitter receptors are concentrated within the postsynaptic active zone, the density of postsynaptic receptors seems much lower than at the neuromuscular synapse (Lisman and Harris, 1993). As a result, total number of receptors activated during the release of the contents of a synaptic vesicle is fewer, and the resulting electrical currents are correspondingly smaller. For example, at CNS synapses using glutamate as a transmitter, the unitary synaptic current produced by the release of the contents of a single synaptic vesicle is approximately two orders of magnitude smaller than that produced by acetylcholine at the neuromuscular synapse (Stevens, 1990). These unitary currents also are much more variable in amplitude, perhaps because of the small and more variable number of receptors (Lisman and Harris, 1993).

The PF synapse has two different classes of glutamate receptor—not only ionotropic receptors that are directly coupled to ion channels, but also metabotropic receptors

that activate G proteins and phospholipase C to produce two intracellular messengers, inositol 1,4,5-trisphosphate and diacylglycerol. These two receptors occupy different regions within the active zone; while the ionotropic receptors are in the center of the active zone and sense high concentrations of glutamate, the metabotropic receptors are found at the peripheral edges of the active zone and are sensitive to lower concentrations (Nusser et al., 1994). This arrangement allows the ionotropic receptors to immediately sense glutamate release, while activation of metabotropic receptors is delayed. The molecules involved in the clustering and segregation of receptors at CNS synapses are not well known but are unlikely to involve the 43 kDa protein so essential for acetylcholine receptor clustering at the neuromuscular synapse. For the case of glycine receptors, a strong case has been presented that a cytoplasmic protein, gephyrin, is involved (Kirsch et al., 1993). For the NR1 subunit of NMDA-sensitive glutamate receptor, a self-association domain in the receptor may promote clustering (Ehlers et al., 1995). Another subunit of the NMDA receptor, NR2, binds to the 95 kDa protein of the postsynaptic density (Kornau et al., 1995). This association may also help cluster receptors, organize the postsynaptic density, or both.

Sensory "Ribbon" Synapses

Ribbon synapses are found in certain primary sensory cells, such as photoreceptors and mechanoreceptors. These synapses are identified by the presence of a proteinaceous ribbon within their presynaptic terminals (Figure 3). Because all of the synapses that possess ribbons tonically release neurotransmitters, it is likely that the ribbon is a structural specialization that allows constant calcium-regulated secretion of transmitters.

The form of the presynaptic ribbon varies among synapses and, in general, is not really the simple linear element implied by its name. In photoreceptor neurons, it is a curved planar sheet of protein (Rao-Mirotznik et al., 1995), while in mechanoreceptor (hair) cells, it is spherical in shape (Roberts et al., 1990). Because ribbons have a larger surface area than the docking areas of the presynaptic membrane, it has been proposed that the ribbons act as collectors of synaptic vesicles and rapidly resupply new vesicles to the docking sites as these sites lose vesicles during exocytosis. While the active zones of photoreceptor neurons have a larger number of docked vesicles than any other presynaptic terminal (Rao-Mirotznik et al., 1995), this attractive interpretation of ribbon function has not yet been tested experimentally.

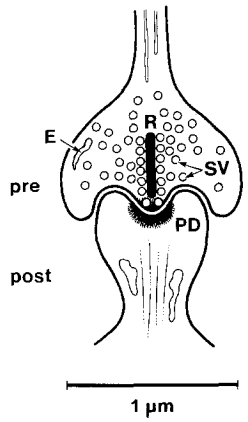

Figure 3. Schematic Structure of a Ribbon Synapse from a Mammalian Photoreceptor

The hallmark of these synapses is a curved, planar proteinaceous structure that appears as ribbon (R) in cross section. Other abbreviations: SV, synaptic vesicles; E, endosomes; PD, postsynaptic density.

Other than the presynaptic ribbon, there appear to be few other structural specializations of ribbon synapses. The presynaptic calcium channels of hair cells are organized in a ring surrounding the spherical ribbon, an arrangement that appears to favor triggering of transmitter release by calcium entering from many open channels (Roberts et al., 1990). The general kinetics and calcium dependence of exocytosis at ribbon synapses seem similar, if not identical, to that of other fast-secreting synapses (von Gersdorff and Matthews, 1994a; Heidelberger et al., 1994). The few reports of endocytosis in presynaptic terminals possessing ribbons suggest that this process may be regulated by calcium (von Gersdorff and Matthews, 1994b) and other cytoplasmic factors (Parsons et al., 1994) in ways different from what has been found in other presynaptic terminals (Schweizer et al., 1995). The postsynaptic structures at ribbon synapses are similar to those of the other synapses described above.

Slow-Acting Synapses

While all of the above-mentioned types of synapses are specialized to transmit rapidly, other types of synapses act over slower time scales. These slow synapses typically release peptide or amine transmitters from dense-cored synaptic vesicles. As an example of such a synapse, we will consider the synapses formed between autonomic neurons and smooth muscle cells (Figure 4). While these neurons secrete a variety of neurotransmitters—including acetylcholine, catecholamines, ATP, and peptides—we will focus on the sympathetic neurons that secrete catecholamines and ATP. Repetitive activation of these neurons produces slow contractions in the postsynaptic smooth muscle cells.

Presynaptic terminals at these synapses are varicose in structure and filled with dense-cored vesicles of various diameters (Burnstock and Hokfelt, 1979; Basbaum and Heuser, 1979). These vesicles are dispersed throughout the presynaptic cytoplasm, and there are no indications of the active zones found in the other types of synapses summarized above. Despite this relative lack of structural compartmentalization, the presynaptic terminal of slow-acting synapses still manages to release transmitters via exocytosis and retrieve vesicle components via endocytosis (Basbaum and Heuser, 1979). At low frequencies of stimulation, vesicle fusion events are rare; high frequency repetitive stimulation is necessary to elicit significant exocytosis, and even under these conditions, no more than one vesicle fuses per varicosity (Astrand and Stjarne, 1989). This pronounced frequency dependence is consistent with the idea that presynaptic calcium channels are distant from the sites of vesicle fusion.

Another structural feature of slow-acting synapses is the

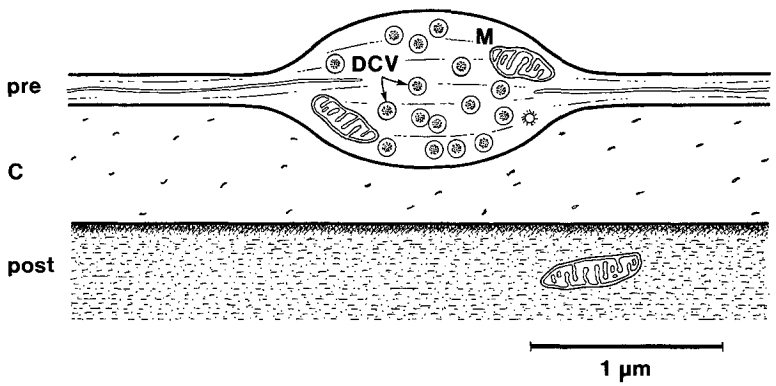

Figure 4. Schematic Structure of a Slow Synapse between a Mammalian Sympathetic Neuron and a Smooth Muscle Cell

This synapse is characterized by a wide synaptic cleft (C) and a presynaptic bouton filled with dense-cored synaptic vesicles (DCV) but lacking a defined active zone structure. The postsynaptic muscle cell also lacks a postsynaptic density. M, mitochondria.

width of their synaptic cleft, which is larger than at other types of synapses and can be as great as 2 μm (Burnstock and Hokfelt, 1979). It would be expected that wide synaptic clefts might produce delays in transmission due to an increased distance for neurotransmitter diffusion; indeed, the rise and decay times of postsynaptic electrical currents at the sympathetic neuromuscular synapse are approximately 10-fold slower than at the frog neuromuscular synapse (Astrand et al., 1988). In addition, there are no obvious postsynaptic densities at these synapses, consistent with the general lack of active zones. Thus, these synapses are optimized for relatively slow and diffuse transmission of electrical signals from presynaptic to postsynaptic cells.

In summary, examination of the structural organization of each synapse described here gives clear insights into the functional specializations of the synapse. Where speed is essential, active zones are present, and small, clear-cored vesicles are used to store fast-acting transmitters. Strong, reliable transmission is produced by presynaptic terminals possessing many active zones and postsynaptic structures with high densities of transmitter receptors, while weaker transmission—more useful for synaptic integration—is characteristic of synapses with fewer active zones and postsynaptic spines. Presynaptic terminals of sensory neurons, which must release transmitters constantly, have evolved the synaptic ribbon to collect synaptic vesicles and efficiently resupply vesicle docking sites.

Structural Dynamics of Synapses

Static images of synapses make it clear that these structures have quite constant and predictable organization. This predicatability serves as the basis for the generalizations summarized above. However, synapses are also capable of undergoing dramatic structural rearrangements under some circumstances. For example, it was mentioned above that presynaptic terminals locally recycle the components of their synaptic vesicles. During recycling, the recent history of exocytosis and endocytosis determines the complement of synaptic vesicles and other membrane-bound organelles (Figure 5). Because these changes occur on a time scale of approximately 1 min (Betz and Bewick, 1992; Ryan and Smith, 1995), structural rearrangement of a presynaptic terminal must be a very dynamic process. Despite these profound structural variations, the overall organization of the terminal is maintained to ensure efficient neuronal communication.

One of the hallmarks of synaptic transmission is its modifiability—a variety of forms of synaptic plasticity are constantly changing the gain of synapses throughout the nervous system. While many of these forms of plasticity alter transmission without producing any obvious structural changes (Zucker, 1989), it is likely that other forms of plasticity are associated with rearrangement of synaptic architecture. Various paradigms that induce long-lasting changes in synaptic strength, including long-term synaptic potentiation, all appear to increase the area of the postsynaptic density and may result in an increase in the number of release sites per bouton (Lisman and Harris, 1993; Bai-

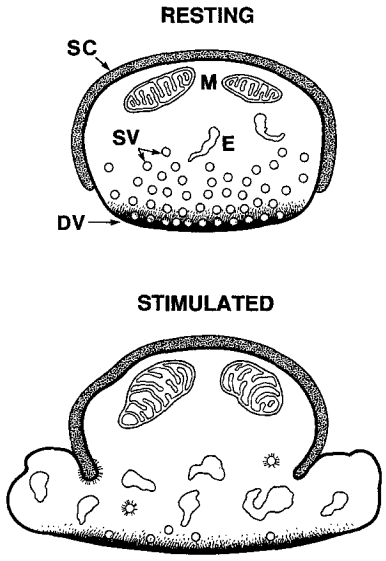

Figure 5. Structural Rearrangements Observed in the Presynaptic Terminal of a Frog Neuromuscular Synapse during Synaptic Activity

Cross sections through presynaptic terminals fixed at rest (top) or fixed after extended presynaptic stimulation (bottom) reveal that stimulation causes a loss of synaptic vesicles and compensatory increases in the surface area of the plasma membrane, coated vesicles and endosomes. Abbreviations: E, endosomes; M, mitochondria; SC, Schwann cell; SV, synaptic vesicles; DV, row of docked vesicles. Adapted from Heuser and Reese (1973).

ley et al., 1994; Edwards, 1995). Structural plasticity is also observed at ribbon synapses during light adaptation in the retina. Adaptation causes horizontal cells to insert postsynaptic spinules, up to 300 nm in length, into the presynaptic terminals of cone photoreceptors. This extension rapidly retracts and disappears after dark adaptation, again indicating a very dynamic remodeling of synaptic architecture (Wagner, 1980).

Conclusions

Although synaptic structure has been studied for decades, many important questions addressing function in terms of synaptic structure have yet to be answered. In particular, our current understanding of the molecular architecture of synapses is very primitive. Along these lines, three general questions seem particularly pressing.

How Is the Structural Precision of Synapses Achieved?

Given that both presynaptic and postsynaptic structures are elaborate assemblies of organelles and molecules, there must be remarkable mechanisms at work to ensure correct assembly of presynaptic and postsynaptic structures.

How Do Presynaptic and Postsynaptic Structures Get Aligned in Space?

The precise registration of a synapse makes it a structural unit. Mechanical homogenization of synapses, during the preparation of synaptosomes, does not prevent the postsynaptic density from remaining attached to the presynaptic process, suggesting mechanical links between the two. One possibility is that proteins extend from each cell and connect to each other, either directly or via the extracellular matrix, to serve as the foundation for transsynaptic alignment. Such alignment molecules could include proteins such as neurexins (Garrity and Zipursky, 1995; Südhof, 1995) or dystroglycans (Sealock and Froehner, 1994).

What Are the Cues for Reorganization during Dynamic Structural Changes?

Several lines of evidence make it clear that synapses are capable of undergoing substantial structural reorganization. However, during these wholesale changes in detailed structure, synapses are still able to maintain their overall structural integrity. Perhaps not unlike the developing synapse (Garrity and Zipursky, 1995; Keynes and Cook, 1995), established synapses are also guided by molecular cues that direct reorganization, although these cues allow the established synapse to remain an architectural unit. Addressing these and other questions about the architecture of synapses should provide interesting challenges and new insights for quite some time.

Acknowledgments

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