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Understanding Synapses: Past, Present, and Future

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Abstract

Classical physiological work by Katz, Eccles, and others revealed the central importance of synapses in brain function, and characterized the mechanisms involved in synaptic transmission. Building on this work, major advances in the past two decades have elucidated how synapses work molecularly. In the present perspective, we provide a short description of our personal view of these advances, suggest a series of important future questions about synapses, and discuss ideas about how best to achieve further progress in the field.

Enormous progress has been made in recent decades in our understanding of synaptic transmission and its use-dependent plasticity. The development of new tools, in particular in molecular genetics, structural biology, electrophysiology, and imaging has led to a detailed understanding of key phenomena, such as the Ca^{2+}-triggering of neurotransmitter release and some of the key mechanisms underlying synaptic plasticity. Nevertheless, major technical and intellectual challenges remain. As *Neuron* turns 20, it seems an appropriate time to provide a brief, highly personal perspective on some of the major advances in our understanding of synaptic function over the last two decades, as well as attempt to point out some of the most important future challenges in an area of research that will continue to be critical for understanding both normal and pathological brain function.

Notable Advances: The Last 20 Years

The last two decades were revolutionary in neuroscience. Years of extraordinary growth and opportunity were provided by expanding technologies, increases in funding, and the realization that understanding the brain is a major, maybe even the most important, frontier in biology. When considering advances in our understanding of synaptic function, much deserves to be noted. However, for reasons of space, we provide a limited list of achievements that reflects our personal bias. This list is thematically organized and not ordered according to perceived importance. Figure 1 provides a schematic illustration of the synapse that highlights some of the points made on the list.

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Defining the Molecular Anatomy of the Synapse

Chronologically, the description of the molecular composition of synapses was the first major step toward understanding the basis of synaptic transmission beyond the elegant electrophysiological studies of pioneers such as Fatt, Katz, Llinas, and Eccles. It is hard to remember now how revolutionary the cloning of the Torpedo nicotinic receptor by Numa was (Noda et al., 1982). This work initiated a 15 year period during which most of the principal components of synapses were purified and cloned. This period started with channels and receptors (e.g., Noda et al., 1982, 1986; Tanabe et al., 1987; Snutch et al., 1990), continued with synaptic vesicle proteins (the first of which was cloned a year before *Neuron* was launched [Südhof et al., 1987]), and was completed with the cloning of synaptic cell-adhesion molecules, active zone proteins, and proteins of the postsynaptic density (e.g., Cho et al., 1992; Brose et al., 1995; Ushkaryov et al., 1992; Ichtchenko et al., 1995). Although the molecular cataloging of synaptic proteins can be viewed as merely descriptive, this work is a prerequisite for understanding synapses. This effort culminated in the systematic analysis of the synaptic vesicle as an organelle (Burré et al., 2006; Takamori et al., 2006), and the development of models for the molecular organization of the presynaptic active zone and the postsynaptic density (Südhof, 2004; Kim and Sheng, 2004; Scannevin and Huganir, 2000; Schoch and Gundelfinger, 2006). Much, however, remains unknown, including a complete list of synaptic cell-adhesion molecules and a detailed understanding of the stoichiometric composition of proteins at different types of synapses.

Understanding the Machinery for Presynaptic Vesicle Fusion

Presynaptic neurotransmitter release is mediated by the Ca^{2+}-triggered fusion of synaptic vesicles with the presynaptic plasma membrane at the active zone (Figure 1). The last 20 years achieved a nearly complete understanding of this process. The description of the synaptic vesicle fusion machine, starting with the identification of synaptobrevin/VAMP as the target of tetanus toxin that is responsible for mediating fusion (Schiavo et al., 1992; Link et al., 1992), not only accounted for how synaptic vesicles fuse, but also provided a blueprint for all intracellular fusion reactions (Jahn and Scheller, 2006). The general principles that apply to all fusion reactions in a cell are simple: a machinery consisting of three or four SNARE proteins and one sec1-Munc18-like protein (SM protein) is positioned and controlled by ancillary proteins, which in the case of the synapse, include active zone proteins such as Munc13 and soluble proteins such as tomosyn (Südhof, 2004).

In parallel, the discovery of synaptotagmin as the synaptic Ca^{2+} sensor that is responsible for the majority of release under normal stimulation conditions in all synapses (Perin et al., 1990) provided a molecular explanation for Katz's pioneering observation that neurotransmitter release is Ca^{2+} triggered (Katz, 1969). This discovery was complemented by the more recent identification of complexin as a cofactor for synaptotagmin in the Ca^{2+} triggering of release (McMahon et al., 1995). A model emerged wherein complexin activates and clamps fusion of synaptic vesicles by binding to partially or fully assembled SNARE complexes (Tang et al., 2006). Ca^{2+} entering the terminal during an action potential then binds to synaptotagmin, thereby inducing the simultaneous interaction of synaptotagmin with phospholipids in the membranes and with the SNARE complex. This interaction displaces complexin from the SNARE complex, bends the phospholipids, and opens the fusion pore (Tang et al., 2006). Many details remain to be clarified in this model; for example, how different synaptotagmin isoforms confer distinct Ca^{2+} affinities and reaction speeds onto fusion (Xu et al., 2007), and whether this diversity is physiologically important. But the fundamental molecular reactions that have been defined are likely to occur in similar fashions in all fast Ca^{2+}-triggered fusion, and account for most of the neurotransmitter, neuropeptide, and hormone secretion observed physiologically.

Long-Term Plasticity: From NMDARs to AMPAR Trafficking

Synapses exhibit marked use-dependent plasticity that manifests as short- and long-term increases or decreases in synaptic strength. Over the last two decades, intense efforts were focused on understanding the mechanisms of NMDA receptor (NMDAR)-dependent long-term potentiation (LTP) and long-term depression (LTD). These efforts were richly rewarded by major discoveries (Lisman et al., 2007). A vigorous debate about presynaptic versus postsynaptic expression mechanisms (Malenka and Nicoll, 1999) led to the resolution that NMDAR-dependent forms of LTP and LTD are both mediated primarily by changes in the number of AMPA receptors (AMPARs) in the postsynaptic density (Shepherd and Huganir, 2007). Depending on the pattern of synaptic activity and the quantitative properties of the resulting NMDAR-mediated rise in Ca^{2+} within dendritic spines, AMPARs can undergo either endocytosis during LTD or insertion into the postsynaptic density during LTP (Figure 1). Much has been learned about the molecular details underlying AMPAR trafficking, such as, for example, the importance of the AMPAR accessory proteins TARPs and scaffolding proteins such as PSD-95 (Chen et al., 2000; Bredt and Nicoll, 2003). However, as sophisticated molecular, imaging, and electrophysiological tools are applied to the study of LTP and LTD, it is apparent that the complexity of the functional roles of even a single protein, such as PSD-95, in these phenomena is daunting (Steiner et al., 2008; Xu et al., 2008).

The Dendrite as an Autonomous Signaling Compartment

Although neurons were known to be functionally and structurally polarized even before Ramon y Cajal provided his beautiful drawings, nobody anticipated the powerful capabilities embodied in dendrites. Studies over the last decades uncovered that dendrites, as the postsynaptic compartment par excellence, can do almost everything the neuronal cell body does, but in a more sophisticated, spatially and temporally compartmentalized manner. Dendrites, or rather various dendritic segments, function as autonomous units replete with signaling elements. We now know that dendrites express a complex array of voltage-dependent conductances, allowing them to generate back- and forward-propagating action potentials. They also contain a full-fledged protein synthesis machinery, including a rough endoplasmic reticulum and a functional Golgi complex (Ehlers, 2007) that are likely critical for the local control of the postsynaptic composition of individual synapses. Dendritic spines, the reception points for most excitatory synapses, are compartmentalized extensions of the dendrites that contain a subset of these elements, and serve as entry points to dendritic signaling. As a result of these properties, dendrites integrate synaptic signals in a nonlinear manner (Bourne and Harris, 2008; Higley and Sabatini, 2008).

Retrograde Endocannabinoid Signaling in Short-Term and Long-Term Plasticity

Many candidate retrograde messengers that might function to carry a postsynaptic signal to presynaptic terminals were advanced over the last decades. However, no consensus molecule emerged until the demonstration that endocannabinoids mediate a phenomenon called depolarization-induced suppression of inhibition (DSI) (Wilson and Nicoll, 2002). During DSI, depolarization of a postsynaptic neuron causes transient suppression of GABA release from presynaptic inhibitory terminals contacting this neuron; this suppression is effected by endocannabinoids that act retrogradely (Figure 1). This seminal finding spawned the discovery of a role for endocannbinoids in several additional forms of postsynaptically induced, but presynaptically expressed, plasticity, especially in long-term plasticity of both inhibitory and excitatory synaptic transmission in various brain structures (Chevaleyre et al., 2006). Strikingly, whereas short-term endocannabinoid-dependent plasticity is independent of the active zone protein RIM1α, long-term endocannabinoid-dependent presynaptic plasticity requires this protein (Chevaleyre et al., 2007; Fourcaudot et al., 2008).

Plasticity in Inhibitory Circuits and Synapses

Recent results revealed the importance of inhibitory synapses in neural circuits, in addition to the traditionally studied excitatory synapses, beyond what was envisioned earlier. Although fewer inhibitory neurons and synapses are present in brain, inhibitory neurons manifest in a bewildering diversity, and their synapses exert a profound influence on the properties of neural circuits (e.g., see Klausberger and Somogyi, 2008). The diversity of inhibitory neurons is not only apparent in their shape and connectivity pattern, but also in the properties of their synapses which, among others, can express multiple forms of LTP and LTD (e.g., see Nugent et al., 2007), besides the endocannabinoid-dependent forms described above (Chevaleyre et al., 2006). Moreover, excitatory synapses on GABAergic interneurons are dynamic and also exhibit a suprisingly diverse repertoire of plasticity (Kullmann and Lamsa, 2007).

The Dynamic Nature of Synapses

Neurons are largely irreplaceable after development, apart from a small population of continuously replenished neurons that originate throughout life from the dentate gyrus and subventricular zone (Zhao et al., 2008). The question of whether synapses are similarly irreplaceable, or can be continuously remodeled during the lifetime of an organism, has been difficult to address. The advent of new imaging tools over the last decade revealed that dendritic spines are very dynamic (Lendvai et al., 2000; Zuo et al., 2005). Long-term in vivo imaging experiments suggested that synapses are continuously formed, eliminated, and remodeled throughout adulthood, although the extent of such processes may vary between different brain regions (Grutzendler et al., 2002; Trachtenberg et al., 2002). Such activity-dependent structural changes in synaptic connectivity likely underlie many forms of experience-dependent plasticity, including learning and memory.

Synaptic Transmission at the Level of a Single Synapse

Major technical advances that went far beyond classical approaches enabled analysis of the exquisite details of synaptic transmission. Such advances included application of capacitance measurements to directly monitor exocytosis from presynaptic terminals, and the use of caged Ca^{2+} that can be released by photolysis (Neher and Marty, 1982; Delaney and Zucker, 1990). Imaging techniques using styryl dyes such as FM1-43, and genetically encoded fluorescent proteins such as synaptophluorin, allowed direct visualization of synaptic vesicle release and cycling (Rizzoli and Betz, 2005). Furthermore, multiphoton microscopy allowed direct visualization and activation of single dendritic spines within intact brain tissue (Mainen et al., 1999; Matsuzaki et al., 2004). These state-of-the-art approaches have made it possible to answer more and more sophisticated questions about synaptic function. Among the major observations emerging from such studies are a more precise definition of presynaptic exocytosis and postsynaptic signaling, the observation of multivesicular release in an active zone, the exact measurements of presynaptic and postsynaptic Ca^{2+} concentrations during synaptic transmission (with some caveats about spatial heterogeneity), and the monitoring of individual vesicles during exocytosis and endocytosis (Wadiche and Jahr, 2001; Murthy and Stevens, 1998; Rozov et al., 2001; Schneggenburger and Neher, 2000; Bollmann et al., 2000; Sun and Wu, 2001; Sun et al., 2007).

Challenges for the 21st Century

We believe there are two types of challenges for research on synaptic function over the next decades: to organize our research efforts in the scientific community effectively, and to use these efforts to answer salient questions about synapses that have the biggest chance of

providing new insights. From our personal perspective, the following questions about synapses are particularly important.

Determining Synaptic Diversity and Its Physiological Importance

Synapses are diverse in shape and properties. We do not know much about how this diversity is determined, nor what it means for the neural networks in which these synapses participate. What determines the receptor composition of individual synapses? How does a synapse become facilitating or depressing during stimulus trains, and what are the molecular underpinnings for this physiological difference? This property is probably related to synaptic cell adhesion since postsynaptic neurons appear to be instructive for presynaptic properties, and vice versa (Maccaferri et al., 1998; Takamori et al., 2000; Rozov et al., 2001), but no molecular mechanisms are known. Identification of the nature and mechanisms that mediate such synapse specification will be important for understanding how neural circuits develop.

Are Learning and Memory Synaptic Events?

While evidence has accumulated that the acquisition of new declarative memories involves long-term synaptic plasticity in the hippocampus, little is known about how they are stored long-term in the cortex. Synaptic changes are likely required for memory formation, as is gene transcription, which may be regulated via epigenetic mechanisms during memory formation and may primarily affect “synaptic” genes (Barrett and Wood, 2008). At least two principal mechanisms are possible by which synaptic mechanisms might store memories: (1) the remodeling of the synaptic wiring diagram by the formation of new synapses and/or the elimination of old synapses, or (2) the selective strengthening and weakening of subsets of synapses without changes in synaptic connectivity. Moreover, memory formation may involve more than synaptic changes, as adult neurogenesis has been hypothesized to be necessary (Leuner et al., 2006). Addressing the role of synapses in learning and memory requires a better understanding of their dynamics, further insights into the connection between the synapse and the nucleus, and better control of the properties of synapses—major challenges that also provide a unique scientific opportunity.

Synaptic Diseases

Because synapses are the fundamental information processing unit in the brain, synaptic dysfunction likely underlies many, if not all, brain disorders. Understanding the pathophysiological mechanisms involved will not only promote our understanding of these diseases and open up new advances in diagnosis and treatment, but may also fertilize progress in understanding synaptic transmission itself. A major challenge over the next decades will be to apply our knowledge of synapses to furthering our understanding of the pathophysiology of neuropsychiatric disorders. This has begun to happen for several prominent diseases, such as, for example, Alzheimer’s disease (Haass and Selkoe, 2007; Viola et al., 2008), autism (Südhof, 2008—see discussion on cell-adhesion molecules below), and drug addiction (Kauer and Malenka, 2007). However, major obstacles to progress remain. Foremost among these is the absence of good animal models for most diseases, the lack of reliable cognitive behavioral assays in mice, and the difficulty of determining whether disorders such as schizophrenia or autism represent a multitude of only distantly related diseases, or a single disease with multiple distinct origins. Thus, therapeutically ameliorating or repairing the synaptic abnormalities underlying brain disorders will remain a daunting challenge that will require further study of the basic molecular mechanisms of synaptic function and plasticity.

Synaptic Cell Adhesion and Synapse Formation

In electron micrographs, presynaptic and postsynaptic specializations of a synapse are always precisely aligned (Lisman and Harris, 1993) and the synaptic cleft between these specializations is filled with electron-dense material. Moreover, biochemically, presynaptic and postsynaptic specializations are difficult to separate from each other. Together, these observations suggest that the presynaptic and postsynaptic sides are connected by *trans*-synaptic cell-adhesion molecules. Many cell-adhesion molecules, including cadherins and ephrins, are linked to synapses (Murai and Pasquale, 2004; Arikkath and Reichardt, 2008). Neurexins and neuroligins, a family of heterophilic cell-adhesion molecules (Ushkaryov et al., 1992; Ichtchenko et al., 1995), are of particular interest because unlike these other cell-adhesion molecules, they are restricted to synapses (Dean and Dresbach, 2006; Craig and Kang, 2007). Despite the description of several types of synaptic cell-adhesion molecules, however, many more such molecules likely remain to be identified, and little is known about precisely what the various cell-adhesion molecules do during synaptogenesis, synaptic transmission, or synaptic plasticity. The precise roles of neurexins and neuroligins are of particular interest here because of their genetic association with autism-spectrum disorders as well as other cognitive and neuropsychiatric diseases (Persico and Bourgeron, 2006; Südhof, 2008). Thus, a major challenge is to identify how synaptic junctions are formed and maintained by cell-adhesion molecules, and how abnormalities in this process lead to neuropsychiatric diseases.

Ca^{2+} Sensors in Neurotransmitter Release beyond Synaptotagmin

Synaptotagmin is the major Ca^{2+} sensor in release that dominates under most stimulation conditions in synaptic and neuroendocrine exocytosis (Südhof, 2004). However, a second Ca^{2+} sensor exists that kicks in at the synapse under rare circumstances; for example, during high-frequency stimulus trains in certain interneurons (Hefft and Jonas, 2005). This second Ca^{2+} sensor normally is dormant in synapses, but can be unmasked in synaptotagmin-deficient synapses in which a biophysical characterization of this Ca^{2+} sensor was achieved (Sun et al., 2007). It appears likely that this Ca^{2+} sensor is evolutionarily older than synaptotagmin, which appeared with the emergence of neurons in cnideria. Moreover, this second Ca^{2+} sensor likely mediates Ca^{2+}-triggered release observed in nonneuronal, nonendocrine cells (Coorssen et al., 1996; Ninomiya et al., 1996). Identifying this second Ca^{2+} sensor for exocytosis will not only fill a major gap in our description of synaptic transmission, but also complete our understanding of the Ca^{2+}-dependent regulation of exocytosis in general.

Mechanisms of AMPAR Trafficking

Activity-dependent modulation of AMPAR trafficking appears to play an important role in a host of adaptive and pathological forms of experience-dependent plasticity. Yet, as mentioned previously, much remains unknown about the precise molecular mechanisms that control the delivery of AMPARs to synapses and their removal. For delivery of AMPARs, a SNARE-based membrane-trafficking machinery must be responsible, likely regulated by Rab proteins (Park et al., 2004) and possibly by a synaptotagmin. The potential role of local dendritic protein synthesis of AMPARs also needs to be elucidated (Steward and Worley, 2002). Moreover, the fate of endocytosed AMPARs and the control over their degradation versus recycling remain enigmatic. Arguably the biggest challenge will be elucidating the complex intracellular signaling machinery by which different levels of Ca^{2+} elevation within spines modulate the equilibrium of AMPAR exocytosis and endocytosis. Of course, similar questions will need to be addressed for other key receptors found at excitatory synapses, including NMDARs and metabotropic glutamate receptors.

Synaptic Plasticity beyond AMPAR Trafficking

It is clear that there are additional forms of long-lasting synaptic plasticity that do not involve AMPAR trafficking. Of particular note are presynaptic forms of LTP and LTD that can be triggered directly by presynaptic signaling machinery activated by changes in presynaptic Ca^{2+} concentration or activation of pre-synaptic G protein coupled receptors such as CB1 (endocannabinoid) receptors. Several of these presynaptic forms of plasticity appear to require the active zone protein RIM1α and the synaptic vesicle protein Rab3, which physically interact with each other to link synaptic vesicles to active zones (Castillo et al., 2002; Chevaleyre et al., 2007; Fourcaudot et al., 2008). However, it is unclear why such a protein complex linking vesicles to the active zone is important. Moreover, the physiological importance of such forms of plasticity is unknown.

More generally, no clear view exists of how many forms of synaptic plasticity there are, and how they are related to each other. For example, do all presynaptic forms operate by the same RIM/Rab3-dependent pathway, similar to the apparent involvement of postsynaptic Ca^{2+} in all forms of postsynaptic long-term plasticity? And, of course, the plasticity of inhibitory synapses remains an important yet relatively underexplored area of research that will certainly become more prominent over the ensuing decades as the importance of inhibitory synaptic connectivity is realized (Klausberger and Somogyi, 2008).

Manipulating Synapses to Explore Circuit Functions

The most important yet daunting task in neuroscience is understanding how the complex neural circuitry of the mammalian brain mediates thought, feelings, and behavior. The ability to precisely manipulate specific synapses, cells, and circuits in behaving animals will be required to face this challenge. Further advances in our understanding of the molecular underpinnings of synaptic transmission and synaptic plasticity, coupled with specific, genetically encoded cell and circuit manipulations will provide new opportunities to perform such manipulations. Over the ensuing decades, we envision that methodologies will be developed that will make it possible to turn on and off transmitter release from specific synapses (e.g., Boyden et al., 2005; Karpova et al., 2005; Adamantidis et al., 2007), or to prevent the occurrence of specific forms of LTP and LTD in a temporally controlled manner. Moreover, molecular manipulation of synaptic cell-adhesion molecules such as neuroligins may make it possible to alter synaptic connectivity between different cell types and brain regions, another potentially powerful approach for studying neural circuit functions. Thoughtful use of such approaches combined with temporal and spatial control of neuronal activity (Zhang et al., 2007) should help begin to answer some of the questions that will certainly challenge and perplex systems neuroscientists throughout this century.

Challenges beyond Pure Science

The conditions under which research is performed have an enormous impact on science, and are rapidly changing. Even if our influence on these conditions is small, we think it worthwhile to briefly mention some key issues that might have dramatic effects on the future of neuroscience research.

What Kind of Neuroscience?

It has been argued that neuroscience is now at the stage of physics in the 1920s when large-scale projects became the best way forward. Large-scale, industrial science employs hundreds of scientists to perform invariant, standardized assays in the service of collecting large data sets with little experimental variability. Indeed, several large-scale biology projects have been very successful, as best exemplified by the human genome project. It is

fascinating to consider large-scale projects that might be useful for neuroscience, for example:

- a systematic cataloging of neuronal cell types in all major brain areas using a combination of electrophysiological, molecular, and microscopy methods
- the generation of conditional alleles and corresponding cre-recombinase expression lines in mice for all neuronal genes
- a neuronal ENCODE project that maps the expression patterns of all genes in brain with the corresponding promoter elements
- a complete 3D reconstruction of a vertebrate brain to determine its complete wiring diagram, analogous to what was done for *C. elegans* by electron microscopy

Such large-scale projects require large budgets, a top-down approach, and a long-term commitment. They have the potential of being transformative by influencing the types of experimental manipulations that can be performed by neuroscientists working at many levels and that therefore can enhance the sophistication of the questions that are being addressed. It would obviously be very powerful to be able, in specific cell types, to express activity sensors, to turn on and off synaptic function and/or plasticity, and to manipulate specific cells' activity in a precise, temporally controlled fashion. The large-scale projects we mention (also see Malenka, 2002) might provide the foundation for achieving these goals. However, such projects are also risky from a cost-benefit perspective.

At this time, we are painfully ignorant about some of the most fundamental questions in neuroscience. How is a single memory encoded by synapses and circuits? How can it last a lifetime? How does activity in specific neural circuits allow the brain to recognize an apple? What neural circuits mediate joy or sadness? It is unclear whether the answers to such questions will arise from large-scale projects, or rather will require attracting the smartest and most creative young scientists to our field to individual projects that they control. Projects such as analyzing the region-specificity of synaptic plasticity, examining the mechanisms involved in such plasticity, and testing the role of plasticity in specific behaviors are likely more effectively performed on a small scale since it cannot easily be scaled up. Overall, the issue boils down to the question of what approaches, in a resource-limited environment, are most cost-effective and most likely to yield important advances.

A related issue is how much basic versus translational (i.e., applied) neuroscience is appropriate. Recently, major opportunities for understanding diseases arose, and political pressures for making use of these opportunities are mounting. It is unclear, however, whether applied neuroscience with a specific goal is more cost-effective than basic, undirected science investigating the underlying biology. Most scientists concur in the need to address medical problems and be guided by diseases. Thus, the challenge will be to organize an appropriate mix of basic and applied neuroscience in each of our laboratories to optimize productivity in the service of the society that provides the resources to conduct the research in the first place. Taking successful projects such as the discovery of the role of hypercholestrolemia and the LDL receptor in atherosclerosis as an example, the ideal situation may be if the direction of basic science is informed by clinical findings, without basic science being forced to work on explaining only these findings. Instead, the hypercholerstolemia example suggests that basic science can be most effective if it unravels the underlying biology that can then form the fundament for clinical applications.

How to Promote Interdisciplinary Research?

Work on synapses will increasingly require interdisciplinary approaches, since these provide the most complete insights. The stunning new methods of the last 20 years, from molecular

manipulations (e.g., mouse genetics and RNAi) and electrophysiological assays (e.g., patch-clamping, tetrode recordings) to sophisticated imaging approaches (e.g., two-photon microscopy) have enabled advances that would have been unthinkable when the first issues of *Neuron* appeared in 1988. This wealth of advances, however, also causes problems.

- Because credit is shared in interdisciplinary research, it is difficult to recruit collaborators. Outside of large-scale projects that receive abundant funding and have defined roles for individual investigators, interdisciplinary collaborations often fail when the participants cannot agree about the distribution of funds and credit.
- Since interdisciplinary research involves techniques that not all participants in a project understand, quality control between collaborators can be difficult. Methods are sometimes insufficiently validated, and their limitations misunderstood. This can lead to conclusions that go far beyond the presented data.
- Publication of interdisciplinary research is difficult. Many papers no longer have any “Experimental Procedures” of note, making an interdisciplinary understanding more difficult. Reviewers are often asked to judge all methods used in a single paper, even if they are familiar with only a few of the methods, leading to either too harsh or, more often, too lenient evaluations.
- In interdisciplinary projects, techniques are often not scrutinized equally and sufficiently, leading to the inappropriate use of techniques that are not yet mature. While it is important to push the envelope and develop novel approaches and hypotheses, exciting new techniques also have limitations, and exciting new findings are sometimes wrong.

Science can be considered “truth by consensus,” and can only progress if all scientists can understand each others’ data. On top of the problems presented by a broadening armamentarium of methods, the difficulty in publishing negative results—especially negative results that contradict previous papers—makes reaching such consensus difficult. Journals often have little interest in hearing that one of their papers is being questioned by other scientists. Moreover, ruling out a hypothesis is often viewed as uninteresting, even if essential for progress.

It would obviously be best not only for interdisciplinary research, but for all neuroscience, if disagreements about data and conclusions could be presented and discussed in a frank, forthright manner. The mechanisms by which to do this are unclear. The Neurotechniques section of *Neuron* is an example of a useful approach to the presentation and discussion of state-of-the-art methods. Additional initiatives that focus on the advantages and limitations of novel approaches and methods will certainly help promote research productivity. Better documentation of experimental procedures would help. The best mechanism for letting scientific communities know about results that are being questioned and becoming controversial is less clear, especially since publicly questioning results and conclusions is often taken personally. Nevertheless, as more and more sophisticated but complex methods are used to probe brain function and more studies involve the use of multiple different approaches, it may benefit the neuroscience community to think about what mechanisms will best help evaluate our progress and determine what should be actively pursued and what should not. Peer review at the journal and granting agency levels has functioned well over the past decades, but may need to be supplemented by additional mechanisms. One possible avenue would be to create a new category of review in which opposing sides of an issue directly argue their cases, supported by data, with the possibility for readers’ comments. Although impossible for a printed journal, such an avenue may be feasible for a web-based journal.

Outlook

In our admittedly biased view, understanding synaptic function is crucial for understanding how the brain mediates thoughts, feelings, and behavior, and what goes awry in neuropsychiatric diseases such as autism and addiction. The synapse forms the minimal computational unit for information processing in the brain, and provides an entry point for understanding the mechanisms of this information processing. For this premise to be confirmed, synapses need to be described at a more sophisticated level—how are they formed, why do they exhibit diverse properties, and what kinds of synaptic plasticity are expressed? Moreover, it will be necessary to specifically manipulate synapses in behaving animals to test the significance of a particular given synaptic property. For example, which forms of synaptic plasticity in what type of synapse are involved in the long-term storage of memories? Furthermore, manipulating synaptic properties and synaptic connectivity with molecular tools will be a powerful approach for testing hypotheses about how neural circuits mediate behavior. Finally, a central goal of research into synapses is to examine the role of synapses in diseases, and the possibility of therapeutically changing synaptic function in novel ways in order to treat, and maybe eventually cure, brain disorders. This is not only important for cognitive disorders such as autism and drug addiction, but also for neurodegenerative diseases, particularly Alzheimer's disease. To achieve the ultimate goals of neuroscience research, synapses certainly must remain a major focus of research for many decades to come.

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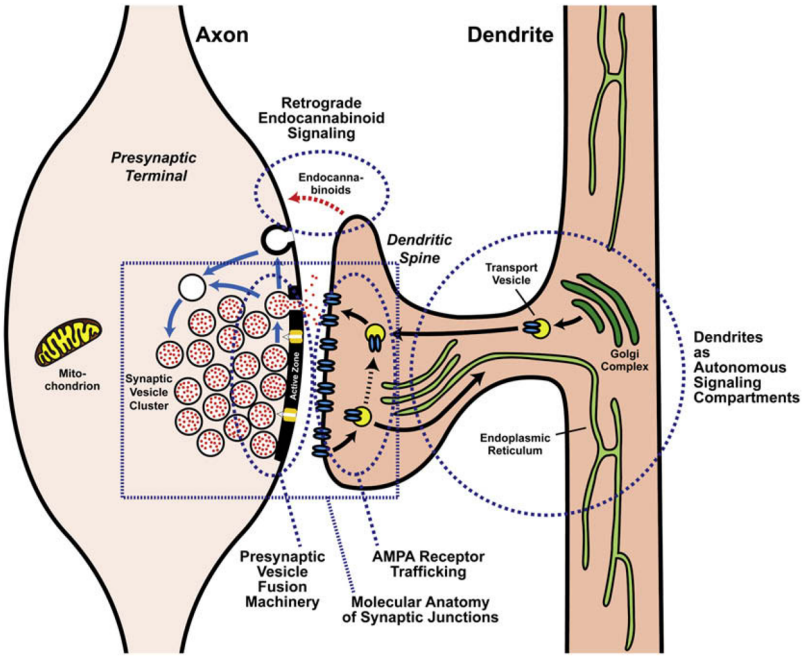

Figure 1. Schematic View of an Excitatory Synapse Formed by an Axonal Varicosity (Left) onto a Dendritic Spine (Right)

Key elements of the apparatus mediating synaptic transmission are indicated, as is the trafficking of postsynaptic AMPA-type glutamate receptors. Some of the major achievements of the last decades are illustrated.