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Perspective

The Dynamic Synapse

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The constant dynamic movement of synapses and their components has emerged in the last decades as a key feature of synaptic transmission and its plasticity. Intramolecular protein movements drive conformation changes important to transduce transmitter binding into signaling. Constant cytoskeletal rearrangements power synapse shape movements. Vesicular trafficking at the pre- and postsynapse underlies transmitter release and receptor traffic between the cell surface and intracellular compartments, respectively. Receptor movement in the plane of the plasma membrane by thermally powered Brownian diffusion movement and reversible trapping by receptor-scaffold interactions has emerged as the main mechanism to dynamically organize the synaptic membrane in nanoscale domains. We will discuss here the different conceptual and methodological advances that have led to a rethinking of the synapse as an organelle whose function is tightly linked to its dynamic organization.

Introduction: Synapses Are Dynamically Organized Elements

Our view of synapse organization has evolved during the past couple of decades from that of a hard-wired element built for fast electrochemical transmission to that of a multiscale dynamic organelle whose function is intimately linked to movement of its individual components in space and time. Hence, neuronal communication must be seen as a dynamic process derived from the integration of the movement of synaptic elements at the intramolecular, intermolecular, and subcellular scales.

After the proposal by Cajal of the discontinuity between neuronal cells (Ramón y Cajal, 1904) and the demonstrations that nerve cells communicate through specialized junctions called synapses (Foster and Sherrington, 1897), the first dynamics of synaptic components was highlighted at the level of the presynapse through the discovery that neurotransmission relies on the fusion of transmitter-filled vesicles with the presynaptic membrane. The importance of membrane trafficking for the function of the presynapse was further reinforced through identification of the complementary endocytic pathway that allows vesicles to be recycled after their fusion (Heuser and Reese, 1973). In parallel, intramolecular protein movement was shown to translate ligand binding to the extracellular domain of certain neurotransmitter receptors into opening of the associated channel through allosteric conformational changes (Changeux, 2012). Up to the end of the 1990s, our picture of the synapse was that vesicles, ions and protein domains were the only elements of synapses whose movements had relevance to fast synaptic transmission. Synapses were envisioned as a two-compartment system with distinct mode of function: a presynaptic element containing vesicles dedicated to fast calcium-dependent fusion and recycling to permit neurotransmitter release in the synaptic cleft and a postsynaptic element containing a hard-coded and invariant number of receptors. Activity-dependent plasticity of synaptic transmission was recognized early as a key property of brain function likely to underlie learning and memory (Bliss and Lomo, 1973). It was then attributed either to presynaptic changes in the efficacy of neurotransmitter release (Bear and Malenka, 1994; Bliss and Collingridge, 1993; Enoki et al., 2009; Lisman, 2003) or to postsynaptic changes in the biophysical properties of the receptors such as conductance or open probability (Banke et al., 2000; Derkach et al., 1999; Scannevin and Huganir, 2000). Neurotransmitter receptors were then thought to be stable in synapses, residing trapped for about the lifetime of the protein; i.e., days to weeks. This stability was believed to account for the robustness of synaptic transmission and the stability of memories, although Lynch and Baudry hypothesized early that some forms of memory could be coded by a change in glutamate receptor numbers (Lynch and Baudry, 1984).

And, yet, even at this time, there were hints from other research fields, such as cell biologists, that the synapse was more dynamic than this cartoon view. More than 40 years ago, membrane biophysicists highlighted the molecular dynamic within membranes (Singer and Nicolson, 1972) related to thermally driven Brownian movement of the embedded proteins. Consequently, diffusion trapping was recognized as the only way to organize membranes. Meanwhile, cell biologists demonstrated the power of vesicular membrane recycling to exchange components between subcellular compartments. Curiously, except for the presynaptic vesicle dynamics, most of the neuroscience community remained blind to these then-new concepts emerging from cell biology until the late 1990s, when a series of papers established that neurotransmitter receptors are not stable in the postsynaptic membrane but undergo constant turnover through endocytic and exocytic processes (Bredt and Nicoll, 2003; Carroll et al., 2001; Collingridge et al., 2004; Lüthi

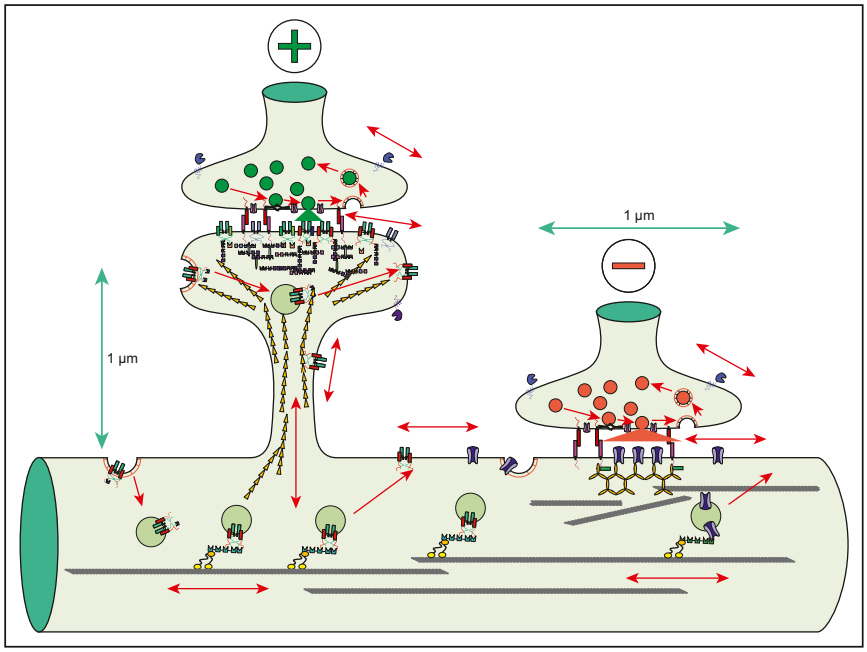

Figure 1. Trafficking Pathways at Excitatory and Inhibitory Synapses

Representation of a piece of dendrite harboring a spine opposed to an excitatory glutamatergic presynaptic terminal (left) next to a shaft inhibitory synapse. The dendritic spines are actin-rich protrusions, which constitute the main site of excitatory connections and form the postsynaptic compartment of most glutamatergic synapses in the mammalian brain. The spine head is separated from the dendritic shaft by a micron long neck about 100 nm wide. Inhibitory synapses using glycine or GABA as a neurotransmitter are always on dendritic shafts or cell bodies. Beside this fundamental difference, the general organization and dynamic properties of both synapse types are very similar. Receptors can traffic either intracellularly (intracellular red arrows) in vesicles bound to microtubules for active transport or on the cell surface by Brownian thermally driven diffusion (extracellular red arrows). Exchange of receptors between the cell surface and intracellular compartments occurs at specific extrasynaptic sites by endocytosis and exocytosis. Presynaptic receptors can also diffuse on the membrane. In the presynapse (top element of both synapses), transmitter filled vesicle exocytosis and recycling is the basis of fast chemical synaptic transmission. This vesicle cycling has been the first demonstration of the dynamic properties of synapses over 40 years ago. At both excitatory and inhibitory postsynapses, receptors are stabilized in front of neurotransmitter release sites through a set of interactions with intracellular scaffold elements enriched in the postsynaptic densities (PSDs) and transmembrane proteins that hold the pre- and postsynapse together. The excitatory PSD is more complex and denser than the inhibitory one, although both display high dynamics and turnover of their constituents. Altogether, regulation of receptor numbers at synapses results from a complex dynamic equilibrium between all subcellular compartments and regulated interactions between the various elements.

et al., 1999; Malenka and Nicoll, 1999; Mammen et al., 1997; Nishimune et al., 1998; Song and Huganir, 2002).

For some years, endocytosis and exocytosis were thought to be the only routes for exit and entry of receptors from and to postsynaptic sites, respectively. In the early 2000s, by unifying the classic Singer and Nicholson model of the membrane and the cell biology of trafficking, we established that lateral diffusion of receptors in the plane of the membrane is a key step for modifying receptor numbers at synapses (Borgdorff and Choquet, 2002; Dahan et al., 2003; Meier et al., 2001; Tardin et al., 2003). In the last decade, a series of studies from our labs and many others established that neurotransmitter receptors are in a dynamic equilibrium between the different subcellular and subsynaptic compartments through the synergy of lateral diffusion and membrane recycling (Triller and Choquet, 2005, 2008). Meanwhile, the concept of the synapse as a dynamic environment was extended to all its components, from its surface membrane to intracellular organelles such as the endoplasmic reticulum (Park et al., 2004) and mitochondria, to its cytoskeletal elements, primarily actin (Matus, 2000), and to its scaffold elements (El-Husseini et al., 2000), enzymes (Shen and Meyer, 1999) and adhesion proteins. Furthermore, the findings that different forms of activity-dependent synaptic plasticity are associated with modifications of the trafficking of either receptors, vesicles or enzymes, has now firmly established that synapses must be understood in the context of their multiscale dynamics at the cellular, intermolecular, and intramolecular levels (Choquet, 2010; Kennedy and Ehlers, 2006; Lisman et al., 2007; Ribrault et al., 2011b; Shepherd and Huganir, 2007) (Figure 1).

Today, the main challenge that lies ahead is to understand the relationship between the above-mentioned different dynamic levels and how they eventually integrate to control neural network activity and, hence, brain function. A starting point toward this end is to determine the characteristic times of the various processes and how they are interconnected and regulated by external stimuli. All cellular and molecular dynamics are governed by thermodynamic laws and can be first approximated through the concept of diffusion reaction within multimolecular assemblies. The membrane, as a two-dimensional diffusional space, represents a simplified case particularly amenable to experimental and theoretical investigations of dynamic processes. In the rest of this Perspective, we will focus our examination on recent progress on the issues related to molecular diffusion and, more specifically, within synaptic membranes.

The Synaptic Membrane as a Dynamically Nano-Organized Space

The neuronal membrane, as any cellular membrane, is a dynamic environment that behaves in first approximation according to the Singer-Nicholson model of the fluid mosaic membrane (Singer and Nicolson, 1972). This model postulated that the membrane is a "two-dimensional oriented solution of integral proteins embedded in a viscous phospholipid bilayer." In this model, membrane proteins and lipids undergo free thermal diffusion in a two-dimensional space. This vision originated, in part, from the observation of diffusion of molecules between cells (Frye and Edidin, 1970) and was further supported by FRAP experiments (Axelrod et al., 1976). However, this model was soon regarded as incomplete, because the measured diffusion

coefficients in biological membranes are more than one order of magnitude lower than those predicted from theory or from measurements in reconstituted lipid bilayers. Work from a number of labs, largely based on high-resolution, single-molecule tracking of proteins and lipids, led to the proposition that the plasma membrane is partitioned into a variety of subdomains, ranging from a few nanometers to microns, within which proteins and lipids are reversibly trapped for varying amounts of time. This partitioning has been proposed to result from the cooperative action of a hierarchical three-tiered mesoscale (2–300 nm) domain: membrane-actin-cytoskeleton-induced compartments (40–300 nm), raft domains (2–20 nm), and dynamic protein-complex domains (3–10 nm). Membrane compartmentalization in subdomains is critical for cell function and distinguishes the plasma membrane from a classical Singer-Nicolson-type model (Kusumi et al., 2012).

In neurons, neurotransmitter receptors have long been known to be concentrated in the postsynaptic density (PSD), a protein-rich subdomain lining the inner surface of the postsynaptic membrane located in front of neurotransmitter release sites. The local enrichment of receptors at PSDs is thought to result from receptor immobilization by stable elements, a concept reinforced by ultrastructural studies that revealed a precise subsynaptic organization of receptors and their associated proteins in the postsynaptic membrane (Triller et al., 1985). This network of molecular interactions has led to the notion of a subsynaptic scaffold between the cytoskeleton and the transmembrane receptors (Garner et al., 2000; Moss and Smart, 2001; Scannevin and Huganir, 2000; Sheng and Sala, 2001). PSD components interact in a biochemical and structural network that functions as a multimolecular machine (Craven and Bredt, 1998; Kennedy, 2000; Kornau et al., 1997; Sheng and Kim, 1996).

Based largely on work at the neuromuscular junction, receptors were initially thought to be very stable in the synapse. The first paradigm shift, however, appeared at the end of the 1990s, when a series of works demonstrated that ionotropic AMPA-type glutamate receptors (AMPARs) could recycle at high rates between the surface plasma membrane and intracellular compartments, limiting the average residence time of receptors at the cell surface to half an hour. This concept was soon extended to all other types of receptors, including NMDA receptors (NMDARs), GABA-receptors (GABARs), glycine receptors (GlyRs), and a variety of metabotropic receptors, which were shown to recycle constitutively and in an activity-dependent manner. Fast modification of receptor numbers at synapses thus appeared as a new mechanism to account for activity-dependent changes in synaptic efficacy (reviewed in Carroll et al., 2001; Malinow and Malenka, 2002).

A second paradigm shift emerged soon thereafter when we demonstrated that both excitatory and inhibitory ionotropic receptors can traffic rapidly at the surface of the plasma membrane by thermally driven Brownian diffusion and exchange between synaptic and extrasynaptic sites (Triller and Choquet, 2003). This was later proven to be a general rule for all neurotransmitter receptors that can diffuse on the neuronal membrane, albeit at various rates. NMDAR have been found to be the more stable receptors (Groc et al., 2006), followed by GlyR and GABAR (Dahan et al., 2003; Jacob et al., 2005), with AMPA and metabotropic receptors being among the most mobile receptors (Borgdorff and Choquet, 2002; Sergé et al., 2002). This finding, together with the observation that sites of receptor internalization and exocytosis lie hundreds of nanometers away from the PSD (Rácz et al., 2004), led to the broadly accepted model that receptor number at synapses results from a dynamic equilibrium between synaptic, extrasynaptic, and intracellular compartments (Triller and Choquet, 2008). The exchange between these various compartments is governed by a tight interplay between surface diffusion and membrane recycling (Figure 1). Surface trafficking of membrane elements is obviously not restricted to proteins of postsynaptic membranes, and numerous examples of fast diffusion have been found for lipids and presynaptic molecules, including syntaxin, integrins, etc.; for example, syntaxin1A was shown to rapidly exchange by means of surface diffusion between synaptic and extrasynaptic regions in rat spinal cord presynaptic terminals. Changes in syntaxin1A mobility are associated with interactions related to the formation of the exocytic complex. Thus, the combination of rapid diffusion with transient localized pauses could alleviate the paradox of the structured but dynamic membrane (Ribrault et al., 2011a).

Key general rules have evolved around the concept of diffusion trapping in the last decade. First, receptors constantly switch on the neuronal surface between mobile and immobile states driven by thermal agitation and reversible binding to stable elements such as scaffold or cytoskeletal anchoring slots or extracellular anchors. Importantly, the rate of receptor diffusion in the mobile state is relatively homogeneous between receptor subtypes, revolving around 0.1—0.5 $\mu m^2/s$. By contrast, the percentage of time spent by a given receptor in the diffusive or immobile state is highly variable, ranging from nearly 0% to about 100%. The average value of this residence time in the mobile or immobile states during the recording session is an important parameter for a given receptor population in a given functional state. This observation is general for all cell membranes and has led to the concept of reversible trapping detailed below (Figure 2).

Second, the membrane is structured and compartmentalized by "pickets" and "fences" consisting largely of submembranous actin creating nonspecific obstacles that restrain the free movement of membrane proteins and weakly confine movement in membrane subdomains of varying sizes, from as big as a whole spine to as small as a few hundreds of nanometers. Third, receptor surface mobility and stabilization is regulated on a wide range of time scales by various stimuli, including neuronal activity, hormones, toxins, pathological states, etc., that have their action mediated largely by expression levels of binding sites ("the immobilization slots") (Lisman and Raghavachari, 2006; Opazo et al., 2012) as well as posttranslational modifications of receptors or scaffold elements. A well-established example at excitatory synapses is the neuronal-activity-dependent stabilization of AMPARs through binding of the C terminus of their auxiliary subunit stargazin to PSD-95. This interaction is regulated by CaMKII-dependent phosphorylation of a stretch of serines in the intracellular domain of stargazin (Opazo et al., 2010; Schnell et al., 2002; Tomita et al., 2005). An analogous example at inhibitory synapses is the regulation by neuronal activity of the diffusion properties of type-A GABARs [GABA(A)Rs] (Bannai et al., 2009). The extracellular matrix (ECM) and adhesion proteins

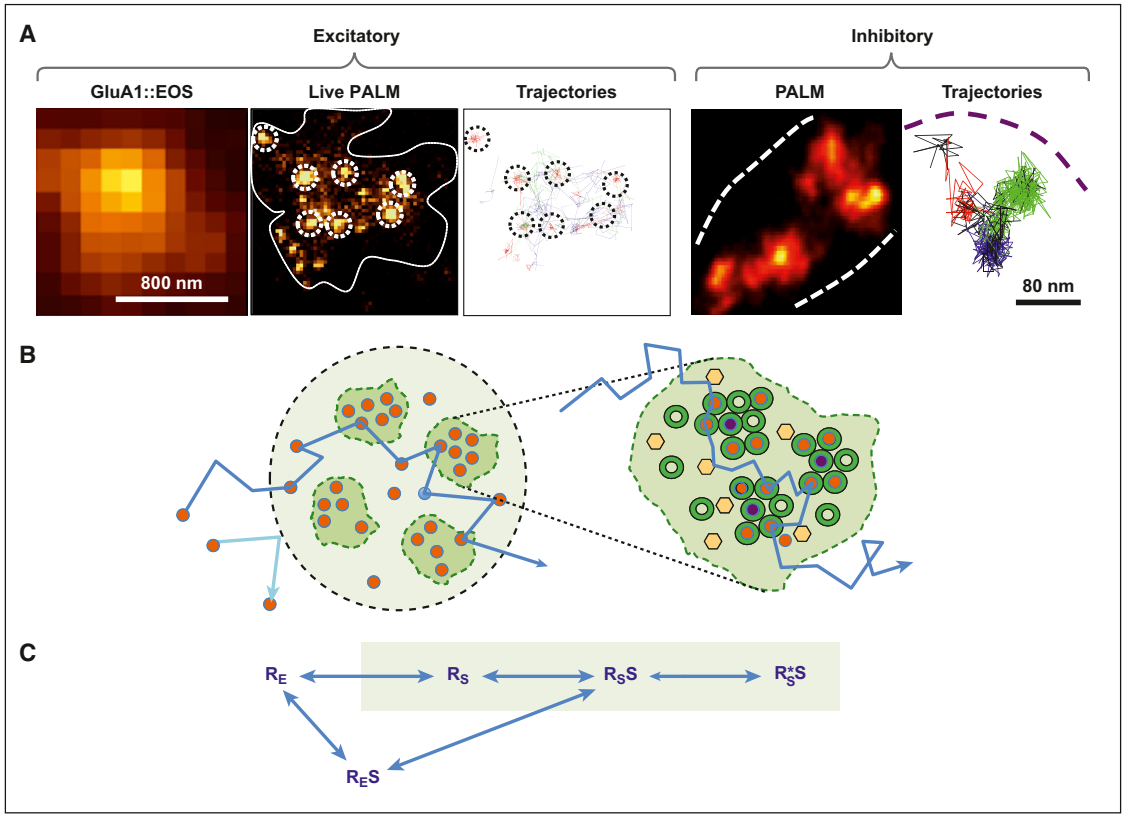

Figure 2. Receptor Diffusion within the Postsynaptic Membrane

(A) Membrane organization and domains.

Excitatory synapse: the left micrograph shows the diffraction-limited, wide-field fluorescence image of the distribution of the Eos-tagged GluA1 subunit of AMPARs at a single spine in a live neuron. Eos is a photo-switchable fluorescent protein. Fine details of GluA1 localization are not evident. The middle micrograph shows the super-resolved image of the same spine reconstructed by photoactivation localized microscopy (PALM) of Eos::GluA1. The nanoscale organization of AMPARs in small clusters is apparent. The right micrograph shows the trajectories of several individual Eos::GluA1 tracked with single-particle tracking PALM in the same spine. Receptors in nanoclusters are immobile (red traces) whereas receptors outside clusters are highly mobile (blue and green traces). Modified from Nair et al., 2013.

Inhibitory synapse: at a given synapse (dotted line), gephyrin forms microclusters (PALM reconstruction using mEos2-gephyrin). SPT-QD trajectory of a single endogenous GlyR swapping from one micro-domain to another with short confinement periods (red-blue-green). White dotted lines represent the synapse border.

(B) Schematic birds-eye view of receptor diffusion at synapses: receptors (orange dot) may enter the postsynaptic membrane area (light green) by lateral diffusion (blue line) or fail to enter (light blue line). Within the synapse, the receptors can enter and exit microdomains with higher scaffold proteins densities (darker green) and then eventually exit the synapse. Right inset: higher magnification of a microdomain. Diffusing receptors (orange dots) may bind or unbind to and from scaffold proteins (green donuts) within nanodomains of higher densities. Receptors in the center of the nanodomains (purple) have difficulty escaping and are thus more stable. Exchanging receptors are likely to originate from the periphery of the nanodomains.

(C) Microscopic reaction rate accounting for receptor (R)-scaffold(S) interactions. Extrasynaptic receptors can be unbound (R_E) or bound (R_ES) to scaffolding proteins; they may enter the synaptic area (light green) as R_S or R_SS. Receptors in the core of nanodomains (R_S^*S) are more stabilized, likely due to multiple interactions (super bound). Underlying reactions are reversible, reflecting molecular scaffold binding-unbinding and molecular crowding, but that from R_S^*S to R_SS is slower.

such as integrins also participate in the dynamic of synapse organization by creating obstacles to the lateral diffusion of receptors, thus modulating short-term plasticity (Frischknecht et al., 2009) or synaptic strength (Cingolani et al., 2008). It was also shown that the β3 subunit of integrin is a key regulator of synaptic scaling and that a crosstalk between β1 and β3 subunits of integrin regulates GlyRs at synapses via a pathway converging on CaMKII (Charrier et al., 2010).

Altogether these rules can be summarized by the concept that diffusion trapping is the major mechanism that can generate molecular heterogeneity in the membrane through reversible binding-unbinding between membrane and submembrane or supramembrane elements. Within this framework, nonspecific corralling of receptors by cytoskeletal elements encourages molecular partitioning, which favors receptor stabilization resulting from binding to specific scaffold elements.

The key parameter for diffusion trapping is the residence time for each molecule within a given interaction. Although residence time reflects in first approximation the affinity of the interaction, recent work has highlighted the important complementary role of multivalency. Indeed, on the one hand, receptors are mostly multimeric complexes that harbor many similar or identical intracellular ligand sequences, while scaffold proteins are also often composed of repeats of similar binding sites. A good example is

again that of stargazin that is present in many copies on a single AMPAR and whose C terminus is a PDZ domain ligand. It binds to the multi-PDZ module scaffold PSD-95 and although the monomeric stargazin-PDZ interaction has a weak affinity in the micromolar range, the multivalent interaction of the AMPAR complex to PSD-95 provides a much more stable interaction (Sainlos et al., 2011).

Diffusional trapping was first studied by diffraction-limited techniques such as FRAP (fluorescence recovery after photobleaching) or by sparse single-molecule tracking in live cells. Although these techniques have provided valuable insight into the concept of reversible receptor stabilization, they have until recently lacked the spatial resolution to investigate the detailed organization of molecules at the molecular scale, particularly in live cells. Electron microscopy (EM) has long provided nanometer level information on synaptic molecule organization, but classical postembedding EM methods have generally lacked the sensitivity to provide exhaustive information on protein distribution. It is only the recent development of optical superresolution methods (Dani et al., 2010) on the one hand and of preembedding EM (Tao-Cheng et al., 2011) or freeze-fracture replica staining methods (Masugi-Tokita et al., 2007) on the other hand that have provided simultaneously the sensitivity and resolution to observe organization of synaptic components at the nanometer scale. All these approaches have come together to establish that neurotransmitter receptors and scaffold elements are often organized in nanodomains rather than diffusively distributed in the synapse (Fukata et al., 2013; MacGillavry et al., 2013; Nair et al., 2013; Specht et al., 2013) (Figure 2A). Conversely, presynaptic molecules and the release machinery are also organized in microdomains as postulated long ago from EM data (Siksou et al., 2007; Sur et al., 1995) and also found recently by optical superresolution microscopy (Pertsinidis et al., 2013).

At excitatory postsynaptic sites, AMPAR subunits are mostly found concentrated in nanodomains < 100 nm in size. These nanodomains are rather stable in time, although individual subunits can enter and exit them by lateral diffusion (Nair et al., 2013). Most interestingly, AMPARs were found to be highly mobile in the synaptic area outside the nanodomains. Hence, our vision of dynamic receptor organization in the synapse must be modified again. Rather than a continuum of mobile and immobile receptors exchanging between a mobile state outside the synapse and a stabilized stated bound to the scaffold inside the synapse, we must now envision the postsynaptic density as a highly heterogeneous space where individual components are organized in nanodomains (Figure 2B). Receptors in nanodomains are rather stable whereas they can move at much higher rates outside. This finding explains why synapses harbor a relatively high proportion of mobile receptors and has important implications for our understanding of synaptic function and on the interplay between synapse dynamic organization and plasticity as detailed further in the text.

The Synapse as a Small System; the Issue of Synaptic Noise

The small size of the synapse combined with the molecular dynamics observed at this level raises a number of fundamental questions related to long-term "stability" or robustness and plasticity. Understanding the mechanisms that underlie the stability and plasticity of synapses requires a probabilistic approach accounting for the more or less unstable molecular interactions. Thus, the postsynaptic membrane has to be seen as a complex multimolecular assembly containing a large variety of molecules, each of which exists at a given synapse in a relatively small number of copies. Consequently the synapse has to be considered as a nanoscale entity with a dynamic structure reflecting molecular interactions. Indeed, the synapse fulfills specific functions and, as such, enters into the category of "small systems" within the mesoscopic realm. It must be the aim of future research to (1) access quantitative parameters related to the synaptic structure; (2) determine quantitatively the number of molecules involved, their dwell times in the synaptic domain, and their diffusion behavior; and finally (3) determine the energies involved in molecular interactions within and outside of synapses (Figure 2C).

There has been some progress in this direction already. We already know that the size and shape of synapses and their subdomains are variable. The diameter of synapses ranges between 200 and 800 nm (m = 300–400) (Carlin et al., 1980; Schikorski and Stevens, 1997; Sheng and Hoogenraad, 2007; Siksou et al., 2007). As seen from a bird's eye view, their global shape can vary, being macular, more or less elongated, having the form of a donut, or that of a horseshoe (Carlin et al., 1980; Chen et al., 2005; Triller and Korn, 1982). Superresolution approaches on unfixed neurons have revealed that inhibitory (Specht et al., 2013) and excitatory (Fukata et al., 2013; MacGillavry et al., 2013; Nair et al., 2013) PSDs are organized in submicron domains of 50–80 nm in diameter that can be more or less confluent.

Within the PSD, the numbers of given molecular entities are in the range of tens to a few hundred depending on the brain area, synapse type, and activity status (Ribrault et al., 2011b). At excitatory synapses, the number of NMDA or AMPA receptors ranges between 0 and 20 (Masugi-Tokita and Shigemoto, 2007; Okabe, 2007) and between 0 and 200 (e.g., Nusser, 1999; Nusser et al., 1998) copies, respectively, whereas the number of the scaffolding protein PSD-95 is 200–400 (Chen et al., 2005) and that of the key enzyme CaMKII is 40–120 (Chen et al., 2005). At inhibitory synapses, the numbers or GlyRs and GABARs (Ribrault et al., 2011b)) range between 10 and 100 and 30 and 200, respectively, while that of the gephyrin scaffolding protein is 40–500 (Specht et al., 2013). Yet, the situation is likely to be more complicated than these numbers imply, as we will need to take into account cell and synapse types as well as subunits and splice variants. However, these available data show that at steady state, the number of core PSD-95 and gephyrin scaffolding proteins far exceeds that of the receptors, thus providing an excess of binding sites to accommodate more receptors in case of plasticity events. These additional sites may be either free or occupied by other proteins of the PSD sharing similar binding capacities. For example, PSD-95 can accommodate not only the AMPAR complex through TARP binding, but also adhesion proteins, NMDA receptors, etc. This is also the case for gephyrin, which can accommodate glycine and GABA receptors. Thus, several molecular entities of the synapse compete for

similar binding sites, increasing the complexity of the diffusion-reaction model.

Another important parameter is that of the molecular dwell time at synapses. This parameter contributes to changing the number of receptors at non-steady state when the net molecular flux (entering or exiting synapses) is different from zero and at steady state in setting the level of robustness of synapses. The dwell times derived from single-particle tracking revealed that receptors display relatively complex behavior with a strong heterogeneity even for a given receptor. One can thus observe receptors dwelling in synapses tens of seconds to minutes or longer (Dahan et al., 2003; Ehrensperger et al., 2007; Heine et al., 2008a; Nair et al., 2013). Interestingly, FRAP experiments evaluating the synaptic recovery of fluorescence associated with scaffolding proteins indicate a much slower recovery in the range of tens of minutes (Specht and Triller, 2008).

The diffusion behavior at synapses is not just a slowdown, an increased confinement, and finally a trapping of receptors. Actually, receptors may integrate into synapses already bound to a scaffolding protein, in which case it depends on scaffold-scaffold interactions. Alternatively, freely diffusing receptors (unbound to a scaffold protein) may access a free slot; in other words, they may bind to a scaffold protein already present at synapses (Ehrensperger et al., 2007). Furthermore, diffusion within the synapse may display a complex behavior swapping from one microdomain to another. This behavior needs to be aligned with the inhomogeneous distribution of scaffolding proteins (Fukata et al., 2013; MacGillavry et al., 2013; Nair et al., 2013; Specht et al., 2013), thus defining subdomains within the PSD. Notably, the diffusion and the trapping of the receptor can be regulated by the activity of the neuron via phosphorylation events that tune the scaffold-scaffold (e.g., Charrier et al., 2010) or the receptor-scaffold (e.g., Opazo et al., 2010; Mukherjee et al., 2011; Specht et al., 2011) interactions.

The demonstration that the molecular dynamics of receptor-scaffold interactions can be regulated physiologically (Triller and Choquet, 2008) has reinforced the notion that molecular movements can link physiology and morphology by providing access to the chemistry in the living cell. The measurement of dwell times and the knowledge of the number of copies of each molecular species together with the three-dimensional organization of the molecules will give access to a real chemistry in living cells, a chemistry "in cellulo." In fact, the dwell time within a multimolecular assembly reflects association and dissociation constants. Furthermore, high-density single-molecule imaging and statistical approaches provided access to the energies involved in the trapping of receptors at synapses (Hoze et al., 2012; Masson et al., 2009; Türkcan et al., 2012).

The diffusion trapping of receptors and the dynamics of scaffolding proteins, each with specific physical constraints and properties, is at the origin of time-dependent fluctuations in molecule numbers referred to as a "molecular noise." It reflects the rate of entry and exit of molecules from the PSD. Fluctuations in the number of receptors, which is one of the determinants of the amplitude of the postsynaptic potential (PSP), may account for part of the variability in PSP amplitudes observed between repeated identical patterns of stimulation (Heine et al., 2008a). However, other stochastic processes such as vesicular release, transmitter diffusion, or channel kinetics also contribute to time-dependent PSP variability (Ribrault et al., 2011b). Thus, receptor-associated molecular noise is an important parameter not only in setting the robustness of the synaptic response, but also in accounting for the stochastic molecular interactions among the constituents of the PSD.

This molecular dynamic approach imposes on our vision of synaptic function the need to incorporate new theoretical frameworks to integrate the cooperative effects between the molecular constituents of the PSD and their regulation, as well as to traverse the scale between the behavior of single molecules and tens-to-hundreds of molecules. A model taking into account the chemical potentials has been proposed for the regulation of receptor numbers at a quasi-equilibrium state (Sekimoto and Triller, 2009). The formation and stability of the synapse can then be modeled via Turing instability in terms of diffusion reaction (Haselwandter et al., 2011). Still, more effort will be needed to fully understand the microscopic biophysical determinants of stability and plasticity of synapses that are under non-equilibrium conditions using fluctuation-dissipation approaches (see Ritort, 2008).

Beside these theoretical approaches, the noise (fluctuations) related to dwell time of the molecular constituents of the synapse may fulfill a specific function. Since the "stability" of the synapse is related to a dynamic equilibrium resulting from the concentration of the molecules inside and outside the postsynaptic domain, an increased noise would favor the shift to another steady state (Sekimoto and Triller, 2009). Along such lines, AMPAR diffusional exchange may account in part for the stochastic variability of postsynaptic EPSCs (Heine et al., 2008a). The newly "stabilized" number of receptors being higher or lower would thus correspond to LTP or LTD, respectively.

A next frontier will be to extend similar deep quantification to living tissue where the connectivity is kept intact, thus accessing mechanisms that link the diffusion dynamics of molecules with their topological organization (at the 10 nm nanometer scale) and synaptic function. These novel ways to approach quantitatively the regulation of molecular dynamics in relation to the synaptic function will open new routes not only to physiology but also to access new parameters for synaptic pharmacology.

Functional Consequences of Diffusion for Synapse Physiology and Plasticity

The synapse dynamic is intimately linked to its formation and function. From the start, synapse formation is based on active and rapid cytoskeletal-based movements of growth cones and filopodias at the origin of the future presynaptic and postsynaptic elements. The precise mechanisms of synapse formation involves a coordinated sequence of cell-cell contacts and recruitment of presynaptic release machinery, closely followed by accumulation of postsynaptic scaffolds and receptors. An extensive set of *trans*-synaptic adhesion proteins such as neurexins, neuroligins and LLRTMs, synCAMs and/or the cadherins are involved in initial pre- to postsynaptic contacts, the specific sequence of events remaining to be clarified (Krueger et al., 2012; Shen and Scheiffele, 2010). Differentiation and specialization between excitatory and inhibitory synapses occurs very early on, but the fascinating mechanisms that underlie

partitioning of the various synaptic components between the different categories of synapses are still not fully understood. At the presynaptic side, recruitment of the release machinery mainly occurs in preformed "packets" through active zone transport vesicles, the so-called Piccolo-Bassoon transport vesicles, which can fuse on demand with the presynaptic membrane to rapidly form an active zone (Gundelfinger and Fejtova, 2012; Waites et al., 2005).

In contrast, recruitment of the postsynaptic machinery is thought to rely heavily on the diffusion trapping of components present in the vicinity of the site of initial cell-cell contact. At excitatory glutamatergic synapses, presynaptic beta-neurexin recruits postsynaptic neuroligin1 from a diffuse surface pool within minutes following initial contact (Barrow et al., 2009; Krueger et al., 2012). Neuroligin in turn recruits the postsynaptic scaffolding protein PSD-95, which is accumulated at sites of neurexin-neuroligin interactions within 1–4 hr after initial contact (Barrow et al., 2009; Heine et al., 2008b; Mondin et al., 2011). During this process, PSD-95 molecules are—at least partly—disassembled from preexisting synapses and recruited to nascent sites of neurexin-neuroligin contact, creating direct competition between earlier and newly formed synapses (Mondin et al., 2011). Following recruitment of PSD-95, functional membrane-diffusible AMPARs are trapped within 2–4 hr. This presumably involves their interaction with neuroligin–PSD-95 complexes through auxiliary subunits such as stargazin (Heine et al., 2008b; Mondin et al., 2011). A similar process involving neuroligin2 recruiting gephyrin likely occurs for the formation of inhibitory synapses.

Whereas excitatory and inhibitory synapses coexist within microns on the same dendritic shaft, they exhibit different shapes and molecular compositions (Figure 1). Indeed, several elements of both synapse types are identical or very similar, such as actin or adhesion proteins like neuroligins. Recent work indicates that ligand-dependent phosphorylation of neuroligin subtypes could regulate their binding to specific scaffolds such as gephyrin or PSD-95 (Giannone et al., 2013; Poulopoulos et al., 2009). In conclusion, postsynapse formation depends heavily not only on diffusion-trapping rates, but also on the availability of the components and their respective affinity that is regulated by posttranslational modifications. Hence, equilibrium between diffusion-reaction rates of molecular interactions is at the heart of synapse formation.

The plasticity of mature synapses is a hallmark of learning and memory. It must comply with the paradoxical long-term stability necessary to store memories and high dynamics necessary for their fast encoding. As presented above, a major paradigm shift in the last decade has been the emergence that synapses maintain global stability while their components are in a dynamic equilibrium between subcellular compartments, hence shifting the concept of stability toward that of metastability (Figure 3). Activity-, development-, or environment-dependent changes in the efficacy of synaptic transmission are related to the modification of both synapse composition and biophysical properties of their individual elements. At the presynaptic level, modifications in the properties of neurotransmitter release mostly underlie plasticity. Mechanisms involve modifications of pre-existing elements of the release machinery (e.g., phosphorylation of synaptotagmin-12) (Kaeser-Woo et al., 2013) as well as relocalization of modulatory elements such as calcium channels (Hoppa et al., 2012) or metabotropic receptors (Bockaert et al., 2010; Suh et al., 2008). It is, however, at the postsynaptic level that dynamics of synaptic components have been best demonstrated to account for synaptic plasticity. Numerous examples have been provided in which diffusion-trap processes or their regulation underlies short- or long-term modification of synapse efficacy (Figure 3A). These include reversible binding between receptors and scaffold elements, oligomerization between various synaptic components, and posttranslational modifications of these same elements, leading to changes in diffusion reaction (phosphorylation/dephosphorylation, ubiquitination, etc.).

One of the most striking examples of the implication of synapse dynamics on plasticity derives from the large fraction of mobile AMPARs present inside synapses (Choquet, 2010). AMPAR movements inside PSDs are fast enough to directly impact synaptic transmission in the millisecond time scale (Frischknecht et al., 2009; Heine et al., 2008a) (Figure 3B). Recovery from fast-frequency-dependent synaptic depression at glutamatergic synapses is accelerated by exchange of desensitized AMPARs for naive ones and is not solely due to recovery of transmitter release and/or AMPAR desensitization (Choquet, 2010; Fortune and Rose, 2001; Heine et al., 2008a; Zucker and Regehr, 2002). Furthermore, physiological regulation of AMPAR mobility impacts the fidelity of synaptic transmission by shaping the frequency dependence of synaptic responses (Heine et al., 2008b; Opazo et al., 2010). Reciprocally, accelerating AMPAR diffusion by removing the extracellular matrix suppresses paired-pulse depression (Frischknecht et al., 2009; Kochlamazashvili et al., 2010). The fact that AMPARs are concentrated to form nanodomains could provide the morphofunctional basis for the new concept of AMPAR mobility-dependent postsynaptic short-term plasticity (Nair et al., 2013).

Long-term depression or potentiation at excitatory or inhibitory synapses involves, in one form or another, modification of synaptic molecules, properties, and/or numbers. Our understanding of the implicated molecular mechanisms has evolved in the last two decades from a model dominated by posttranslational modifications of stable molecules leading to changes in their biophysical properties to a refined one in which the same modifications induce primarily a change in their traffic rates, leading to changes in their type/number at synapses.

At excitatory synapses, activity-dependent modifications in AMPAR, NMDAR or Kainate receptor trafficking leading to changes in their accumulation in front of transmitter release site have been largely documented (reviewed in (Anggono and Huganir, 2012; Bard and Groc, 2011; Lisman and Raghavachari, 2006; Opazo and Choquet, 2011)) all the way from cell culture systems (e.g., (Carta et al., 2013; Park et al., 2004; Petrini et al., 2009)) up to ex vivo brain slices (e.g., (Bellone and Nicoll, 2007; Makino and Malinow, 2009; Mameli et al., 2007; Shi et al., 1999)) and even in vivo (Brown et al., 2010; Rao-Ruiz et al., 2011; Rumpel et al., 2005). Altogether, data from many labs favor a three-step mechanism for the regulation of AMPAR numbers at synaptic sites during LTP involving exocytosis at extra/perisynaptic sites, lateral diffusion to synapses and a subsequent rate-limiting diffusional trapping step (Opazo and Choquet, 2011). Conversely, LTD has

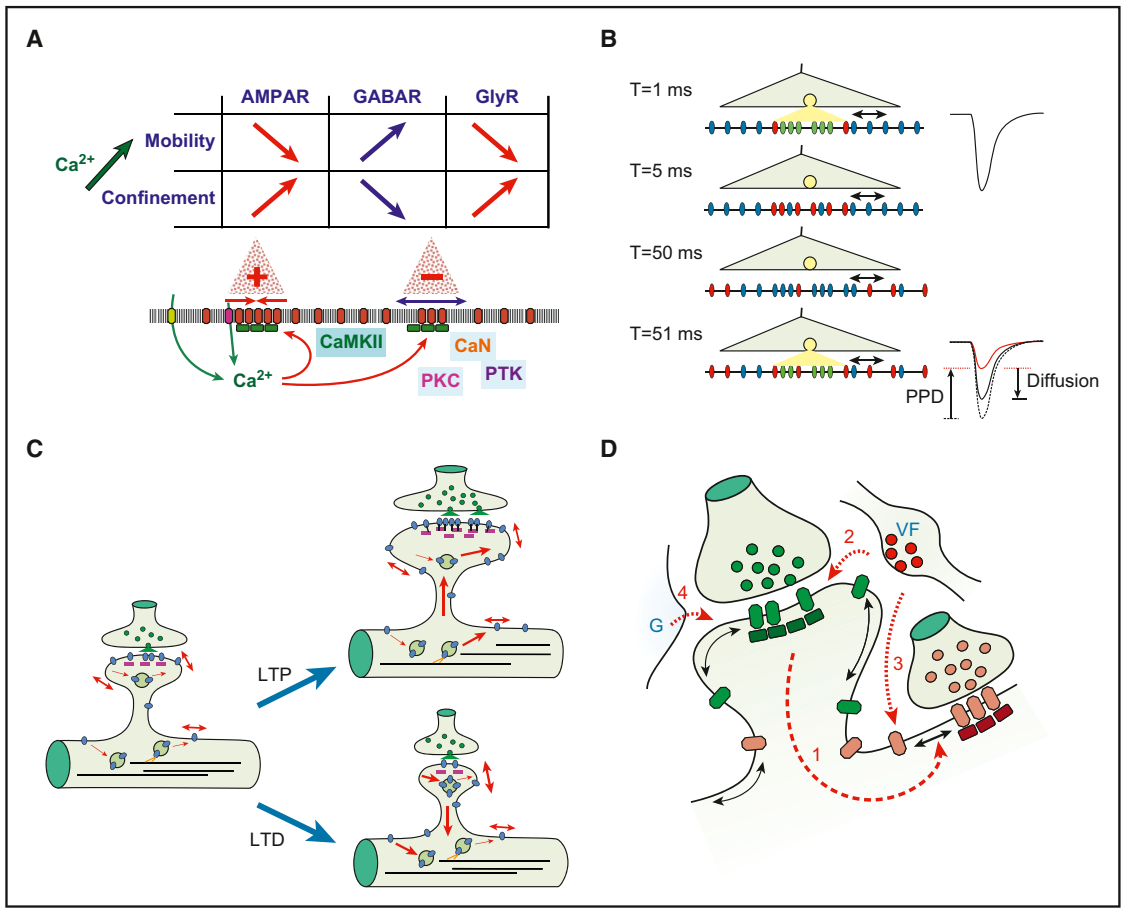

Figure 3. Plastic Regulation of Synaptic Strength

(A) Calcium-dependent regulation of AMPAR, GABA(A)R, and GlyR mobility and confinement at synapses. Lower inset: the increased and decreased confinement leads to increased and decreased receptor numbers at synapses, respectively. Receptor trapping at synapses is regulated by calcium-dependent phosphorylation or dephosphorylation events involving CaMKII, PKC, PTK, and calcineurin (CaN).

(B) Receptor diffusion tunes short-term synaptic plasticity of fast synaptic transmission. The area over which receptors are activated by neurotransmitter (green) is usually limited in space (e.g., 150 nm for AMPAR), and receptors rapidly enter a desensitized state (red) after initial activation. Thus, receptor fast diffusion allows for exchange of desensitized receptors by naive ones (blue), allowing for a faster recovery from short-term synaptic depression due to postsynaptic receptor desensitization.

(C) Changes in receptor trafficking underlie many forms of long-term synaptic plasticity. NMDA-dependent long-term potentiation (LTP) of glutamatergic synapses is mediated by an increase in AMPAR synaptic content due to the consecutive trapping of diffusing AMPARs and exocytosis of new receptors. Conversely, long-term depression (LTD) originates from decreased trapping of AMPARs at synaptic sites and diffusion to sites of endocytosis.

(D) Extrinsic tuning of receptor diffusion-trap: Excitatory events may tune inhibitory receptor lateral diffusion (1). Volume-transmitted molecules may tune the synaptic trapping of excitatory (2) and inhibitory (3) receptors as well as glial-cell-derived factors (4).

been proposed to involve lateral diffusion out of synapses, followed by endocytosis at extra/perisynaptic sites (Groc and Choquet, 2006; Newpher and Ehlers, 2009) (Figure 3C). These different trafficking steps are regulated during synaptic plasticity and their detailed description is beyond the scope of this review. As a representative example, changes in the synaptic accumulation of AMPARs at synapses have been suggested to be a major substrate for NMDAR dependent LTP (Choquet, 2010; Kennedy and Ehlers, 2006; Lisman et al., 2007; Shepherd and Huganir, 2007). LTP at CA1 synapses in the hippocampus is initiated by the influx of Ca^{2+} through NMDAR into dendritic spines. The synaptic increase in AMPAR number at synapses is likely to be a multistep process including their exocytosis from endosomes to extrasynaptic membranes (Kennedy et al., 2010; Yudowski et al., 2006), lateral diffusion of receptors into the synapse, and their subsequent trapping. The relative timing of AMPAR exocytosis during LTP is still ambiguous, and we and others (Makino and Malinow, 2009; Opazo and Choquet, 2011; Opazo et al., 2010; Tomita et al., 2005) have proposed that synaptic trapping of pre-existing surface receptors through rapid (sub-second) CaMKII induced phosphorylation of TARPs is the first event of potentiation. Regulated exocytosis of AMPARs occurs on a slower (tens of seconds) time scale and recruits other signaling pathways that may involve the ras-ERK pathway (Patterson et al., 2010) and Band 4.1 (Lin et al., 2009).

Similarly, plasticity of inhibitory synapses involves regulation of the traffic of GABA(A)Rs or GlyRs (reviewed in Luscher et al., 2011; Ribrault et al., 2011b) by activity-dependent and

cell-type-specific changes in exocytosis, endocytic recycling, diffusion dynamics, and degradation of receptors. As for the glutamate receptors, these regulatory mechanisms involve receptor-interacting proteins, scaffold proteins, synaptic adhesion proteins, and enzymes (Figure 3A). For example, neuronal activity modifies diffusion properties of GABA(A)Rs in cultured hippocampal neurons (Bannai et al., 2009). Enhanced excitatory synaptic activity induces a loss of GABA(A)Rs from synapses and concomitant reduction in GABAergic mIPSC through increased surface mobility depending on Ca^{2+} influx and calcineurin activity. Gephyrin dispersal is not essential for this GABA(A)R declustering (Niwa et al., 2012). Altogether, this indicates that GABA(A)Rs diffusion dynamics are directly linked to rapid and plastic modifications of inhibitory synaptic transmission in response to changes in intracellular Ca^{2+} concentration triggered during high-frequency excitatory stimulation (Bannai et al., 2009; Muir et al., 2010). Thus, long-term depression (LTD) of unitary IPSCs is tightly linked to stimulation-induced LTP of excitatory synapses through regulation of GABA(A)R diffusion trapping, i.e., GABA(A)R-gephyrin interaction.

Finally, long-term homeostatic regulation of neuronal activity through the process of scaling that bidirectionally and proportionally adjusts postsynaptic AMPAR abundance to compensate for chronic perturbations in activity has also been recently shown to involve changes in diffusion-reaction rates (Tatavarty et al., 2013). Scaling down synaptic transmission decreases the steady-state accumulation of synaptic AMPARs by increasing the rate at which they unbind from and exit the postsynaptic density.

Modulatory Mechanisms of Diffusion at Synapses and Potential Relevance to Disease

Synaptic dysfunction has recently appeared to be at the basis of several severe brain pathologies. This has led to define the term ''synaptopathies,'' diseases relating to the dysfunction of the synapse. Examples include autism spectrum disorder, schizophrenia (Ting et al., 2012), and Alzheimer's (Selkoe, 2002). As detailed above, diffusion and/or trapping of many synaptic molecules such as receptors, scaffolds, adhesion proteins, etc., are intimately linked to their role in synaptic transmission. For example, receptors are only functionally relevant to synaptic transmission when located in front of transmitter release sites, whereas scaffold numbers and location set receptor stabilization at given sites at the surface or inside the neuron. Hence, it is tempting to speculate that on the one hand, anomalies in synaptic molecule diffusion trapping are at the origin of some synaptic dysfunction and consequently some brain diseases; on the other hand, finding ways to pharmacologically regulate diffusion or trapping may provide new targets for drugs to tune receptor accumulation at synapses or to prevent the deleterious action of pathological proteins (e.g., misfolded proteins).

Although direct causative links are still missing, variations in receptor diffusion have already been linked to various pathological states. Thrombospondin-1 (TSP-1), a large extracellular matrix protein secreted by astrocytes during development, inflammation, or following brain injury (e.g., DeFreitas et al., 1995; Lin et al., 2003), that has been involved in functional recovery after stroke (Liauw et al., 2008) reduces the lateral diffusion-dependent accumulation of excitatory AMPARs, increases that of inhibitory GlyRs in synapses, and counteracts the increased neuronal excitability and neuronal death induced by TNFα released after brain injury (Hennekinne et al., 2013). Another example is that of fibrinogen, a ligand for β1 integrin, which is released following the rupture of the blood-brain-barrier and which increases the escape of inhibitory receptors from synapses (Charrier et al., 2010), thus favoring excitotoxicity. Along the same line, the stress hormone corticosterone, which inhibits synaptic plasticity, increases the GluA2 containing AMPAR surface mobility and synaptic GluA2 content in a time-dependent manner (Groc et al., 2008). Furthermore, some pharmacological agents such as the cognitive enhancer and antidepressant Tianeptine favor synaptic plasticity and reduce the lateral diffusion of AMPARs (Zhang et al., 2013). This effect involves a CaMKII-dependent enhancement of the PSD-95-stargazin interaction and prevents increases of AMPAR diffusion by corticosterone. Thus, the mechanisms related to the diffusion trapping of receptors are targets for pharmacological actions aimed at controlling the excitation-inhibition balance.

In another domain, although still controversial, a large body of evidence suggests a toxicity of soluble amyloid β (Aβ) oligomers in the memory impairment characteristic of Alzheimer's disease. The effect of Aβ extracellular oligomers could be related to their interaction with the neuronal plasma membrane. For example, AMPAR removal underlies Aβ-induced synaptic depression and dendritic spine loss (Hsieh et al., 2006). This could originate from the observation that Aß oligomers diffuse together with mGluR5 receptors to which they are bound, leading to the formation of aberrant clusters at the origin of the removal of NMDA receptors from synapses (Renner et al., 2010). Aβ oligomer- and mGluR5-dependent ATP release by astrocytes may further contribute to the overall deleterious effect of mGluR5 receptors in Alzheimer's disease (Shrivastava et al., 2013). The extracellular Aβ oligomers also bind to PrPc to generate mGluR5-mediated increases of intracellular calcium that finally disrupt neuronal function (Um et al., 2013). Altogether, these observations implicate diffusive processes in the physiopathology of diseases.

Conclusion

The concept of the dynamic synapse emerged nearly 40 years ago (Heuser and Reese, 1973), and already 30 years ago, Lynch and Baudry postulated that ''the postsynaptic face of the neuronal connections is quite plastic and can be substantially changed by physiological activity'' (Lynch and Baudry, 1984). Despite enormous progress, much remains to be discovered about the interplay between synapse dynamics and function in both normal and pathological conditions. Future aims will focus on integrating synapse dynamics within the framework of brain function, neuronal network, and network dynamics. New technologies give access to the ability to analyze simultaneously the dynamics of a large number of molecules while the physiology is monitored. High-density data and new analytical methods already provide real time 3D recording of molecular movements at the single synapse level. Soon, smaller and brighter intelligent probes will advance these measurements in 3D to integrated systems ex vivo in brain slices and even in vivo. This will generate large amount of data, urging the need for the

development of new analytical methods and a theoretical framework derived from statistical thermodynamic. Finally, integrating synapse dynamics with signaling pathways and function opens the door to our understanding of synapse-dysfunction-related diseases.

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