Surface trafficking of receptors between synaptic and extrasynaptic membranes: and yet they do move!

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Concentration of neurotransmitter receptors at synapses is thought to result from stable binding to subsynaptic scaffold proteins. Recent data on synaptic plasticity have shown that changes in synaptic strength derive partly from modification of postsynaptic receptor numbers. This has led to the notion of receptor trafficking into and out of synapses. The proposed underlying mechanisms have under-evaluated the role of extrasynaptic receptors. Recent technological advances have allowed imaging of receptor movements at the single-molecule level, and these experiments demonstrate that receptors switch at unexpected rates between extrasynaptic and synaptic localizations by lateral diffusion. Variation in receptor numbers at postsynaptic sites is therefore likely to depend on regulation of diffusion by modification of the structure of the membrane and/or by transient interactions with scaffolding proteins. This review is part of the TINS Synaptic Connectivity series.

Introduction

New imaging methods now allow visualization of receptor movements at the single-molecule level inside and outside synapses. They have revealed that receptors permanently exchange between synaptic and extrasynaptic locations. This has changed our view of the organization of the neuronal membrane, which now includes lateral diffusion of receptors as a key parameter for regulation of synapse function and plasticity. As a consequence, extrasynaptic pools of receptors are likely to have a more important role than previously suspected. The aim of this review is to highlight this point.

Until recently, ultrastructural immunocytochemistry has provided the backbone of our knowledge on the distribution of receptors in neurons. The first receptor to be seen using electron microscopy concentrated at synaptic sites was that for glycine [1], and it was followed by many others [2,3]. This morphological approach has established that most receptor types are concentrated at synapses [4]. The ratio between the numbers of synaptic versus extrasynaptic receptors was generally found to be higher in morphological experiments than in physiological experiments, which generally detect more extrasynaptic receptors (e.g. see Refs [5,6]). This discrepancy resulted from the failure of immunocytochemistry to detect receptors at low density, such as in the extrasynaptic membrane (Figure 1). The consequences of these discrepancies have been overlooked. Indeed, the total number of surface extrasynaptic receptors is likely to be larger than that of synaptic ones, owing to the large surface area of extrasynaptic versus synaptic membrane [7].

The preferential and specific localization of receptors at synapses has long been postulated to result from their interactions with submembranous scaffolding proteins. The first of these to be characterized at central synapses was gephyrin [8], which is localized below receptor micro-domains at inhibitory synapses [1,9]. Comparison with the neuromuscular junction encouraged the postulate that...
gephyrin is involved in the so-called ‘stabilization’ and ‘concentration’ of the receptors [1]. These two concepts, often unduly mixed, were extended to most central synapses and believed to be the heart of synapse-specific receptor localization. This was reinforced by the discovery and characterization of numerous scaffolding molecules interacting with receptors [10,11]. These structural and biochemical observations have perpetuated the false notion that receptors are fixed at synapses and that this accounts for their concentration. Although electrophysiology has long-since provided evidence for the existence of extrasynaptic receptors [12], they were often thought to pertain to a pool of receptors distinct from synaptic ones. More importantly, their physiological roles have been limited to activation by spillover of neurotransmitter outside the synaptic cleft during massive release [13–15] or during glutamate release by neighboring glia [16]. The notion that extrasynaptic and synaptic receptors are separate entities was reinforced by the fact that some receptor isoforms have specific subcellular distributions. For example, at excitatory synapses, the NR2b subunit of the NMDA receptor is mainly extrasynaptic in the adult, whereas NR2a is detected both inside and outside synapses [6]. At inhibitory synapses, GABA receptors with various subunit compositions have preferential extrasynaptic and synaptic distributions [17].

This classical static view of receptor distribution was challenged a few years ago by evidence that receptor numbers at synapses are tuned during regulation of synaptic strength (reviewed in Refs [18–20]). This is now considered one of the molecular bases of synaptic plasticity and has led to the important notion of receptor flux into and out of synapses, both at rest and during plasticity. It has prompted the development of dynamic real-time imaging approaches in living neurons, such as video-microscopy of green fluorescent protein (GFP)-tagged receptors, to go beyond the fixed snapshots given by immunocytochemistry. However, these multimolecular approaches have limits and, for example, cannot detect receptor fluxes in basal conditions when synaptic receptor numbers remain globally constant. The advent of single-molecule imaging techniques now enables measurement of individual receptor movements in identified submembranous compartments, and reveals the heterogeneities and new physical parameters important for the understanding of receptor trafficking.

**Evidence for rapid traffic of synaptic receptors**

Rapid activity-dependent appearance or disappearance of receptors at synapses has been established for GABA and glutamate receptors. The mechanisms underlying these rapid changes involve exocytosis and endocytosis of receptors (reviewed in Refs [18–21]). Until recently, changes in receptor numbers at synapses were mainly considered as cycling between surface and intracellular compartments. Thus, attention has been drawn to intracellular receptors, and large intracellular pools of receptors have indeed been detected in dendrites using light and electron microscopy [22]. Receptors can accumulate in these intracellular stores following transport from the soma, local synthesis (e.g. Ref. [23]) or endocytosis. This intracellular pool is thought to correspond to receptors that directly exchange from and to synapses, both during basal turnover and stimulated trafficking. In some instances, a specific reserve pool of intracellular receptors seems to be mobilized upon neuronal activity [24–26].

However, two sets of observations indicate that most membrane traffic occurs outside synapses. First, sites of endocytosis, revealed through coated pit formation, are observed mainly outside the synaptic areas using light or electron microscopy [27–29]. At some synapses, multiple subtypes of receptors coexist and form intricate mosaics [3,4]. During plastic processes, some subtypes are removed by endocytosis. This implies sorting of receptors before internalization [21], which might occur by specific receptor diffusion out of the synapse and subsequent capture by extrasynaptic coated pits [30,31]. Along this line, elegant experiments using AMPA receptors tagged with a pH-sensitive form of GFP recently showed that NMDA-induced removal of AMPA receptors from synapses is preceded by transient endocytosis of extrasynaptic AMPA receptors [32]. Second, some synaptic receptors are not inserted directly at synapses during constitutive or activity-dependent exocytosis [33]. Thus, receptor diffusion into and out of synapses before and after membrane traffic events are an additional step in understanding the specific receptor trafficking that accounts for changes in receptor numbers at synapses (Figure 2).

The role of lateral diffusion in regulation of receptor numbers at synapses has also been highlighted by physiological experiments. At glutamatergic synapses, NMDA-receptor-mediated excitatory postsynaptic currents show anomalous recovery following ‘irreversible’ block by MK-801 [34]. The recovery could not be attributed to unbinding of MK-801 or to insertion of new receptors, suggesting that membranous receptors had moved laterally into the synapse. A more recent example involves glutamatergic synapses in the neonatal hippocampus [35].

![Diagram](https://www.sciencedirect.com)
Although most of these developing synapses have both AMPA and NMDA receptors [36], the AMPA-sensitive but not the NMDA-sensitive component is extremely labile and can be lost after a brief synaptic activation. This could explain the silencing of AMPA synapses. The rapidity and selectivity of this removal is hard to reconcile with direct endocytosis at synapses and is better explained by lateral diffusion of receptors out of synapses.

Fast activity-dependent changes in receptor number at synapses have been documented during protocols of long-term potentiation (LTP) (e.g. Refs [24,25]), experience-dependent strengthening of transmission [37] and long-term depression (LTD) [38–40], and following pharmacological manipulations [30]. These changes could involve lateral migration of receptors to or from synapses. For LTP induction, a recent paper [41] described an increase in the number of extrasynaptic AMPA receptors that could then be translocated to synapses. During LTD, an opposite mechanism could account for the decrease in numbers of postsynaptic receptors. Dissociation of AMPA receptors from the postsynaptic density (PSD) and consecutive movement to the extrasynaptic membrane could be followed by entry in the constitutive endocytic pathway [30,31]. Indeed, synaptic AMPA receptor number is regulated by glutamate itself, which increases AMPA receptor internalization [21,30,42]. Interestingly, it has recently been shown that glutamate induces dissociation of AMPA receptors from stargazin, itself being stabilized at synaptic sites by its interaction with PSD-95 [43]. Diffusion of receptors can therefore account for rapid changes in receptor numbers at synapses. The long-term modifications observed in LTP or LTD could result from determination of a new set-point in the dynamic equilibrium between synaptic and extrasynaptic receptors. This could involve modification of the number of scaffold molecules or of receptor–scaffold interactions. Similarly, disruption of the subsynaptic cytoskeleton using pharmacological tools leads to destabilization of the postsynaptic inhibitory receptor clusters [44]. Here again, disappearance of receptors from synaptic sites can be interpreted as a dilution in the plasma membrane.

Altogether, these data point to the need for a pool of extrasynaptic receptors for regulation of synaptic receptor numbers. We now suggest that the biology of extrasynaptic versus synaptic receptors should be envisaged in the framework of homeostatic regulation of receptor numbers at synapses, mediated by exchanges between synaptic and extrasynaptic membranes (Figure 3a). This is likely to be true for most receptors. The emerging concept that synaptic receptors are cycling into and out of the synapse both at rest and during plasticity calls for review of the functional role of nonsynaptic receptors: synapses behave as donors or acceptors for receptors, and the extrasynaptic complement of receptors is the reserve pool.

**Direct visualization of receptor movements and regulation by scaffold proteins**

Recent results indicate that glycine receptors [45,46], GABA receptors (S. Le´vi, personal communication), and AMPA [31] and NMDA [47] glutamate receptors are all mobile in synapses and can be exchanged between synapses through lateral diffusion in the plane of the extrasynaptic plasma membrane.

The initial concept, according to which receptors can enter and leave synaptic sites through lateral diffusion, was established at the neuromuscular junction [48]. A role for diffusion of receptors in the plasma membrane was first postulated as a mechanism for the formation of synapses, during which receptor distribution shifts from low to high local density. Experiments showing that extra-junctional ACh receptors rapidly diffuse in the muscle membrane [48] led to the ‘diffusion-trap’ model, according to which the nerve contact region is a trap for rapidly diffusing receptors in the membrane, thereby concentrating ACh receptors during innervation. This was then forgotten for decades.

Study of receptor trafficking dynamics in the CNS has long relied on use of immunocytochemistry. In the late...
1990s, a series of papers established that neuronal activity could lead to rapid redistribution of receptors from synaptotagmin to nonsynaptic sites [21]. A first attempt at measuring the diffusion rates of surface receptors used thrombin-cleavable extracellular tags [49], and glycine receptor movements along dendrites were found to have a speed of 1–2 μm min⁻¹. A similar approach was used to estimate the translocation rate of the AMPA receptor subunit GluR1 [33]. In the search for alternative techniques to study receptor movements in real time, latex particles (of 0.5 μm diameter) were coupled via antibodies to the extracellular domains of receptors including glycine, AMPA and metabotropic glutamate receptors [46,50,51]. These experiments enabled tracking of extrasynaptic receptors and established that receptor interactions with scaffold protein clusters are transient (tens of seconds). This appeared to be a general behavior and was observed directly for interactions between glycine receptors and gephyrin [46], between GABA receptors and gephyrin (C. Schweizer, personal communication), between metabotropic glutamate receptors and homer [51], and between AMPA receptors and PSD-95 (C. Bats, personal communication). Receptors are constantly moving between, or interacting with, scaffold aggregates at high (10⁻¹–10⁻² μm² s⁻¹) or low (<10⁻⁸ μm² s⁻¹) diffusion rates, respectively. Dwell-time distributions of residency at clusters depended on given receptor–scaffold pairs. This probably reflects the association–dissociation rate of the interaction. The physical characteristics of the diffusion were also different: the movements were Brownian-like between scaffold clusters and were confined when within clusters. Brownian movements are dominated by thermal agitation of molecules and are characterized by a linear dependence of the explored surface versus time. By contrast, confined movements, although also powered by thermal agitation, are more complex and spatially limited by interactions with obstacles of various origins (e.g. scaffold proteins, membrane domains or transmembrane proteins). The reversibility of the association of receptors with clusters could result either from the unbinding of receptors from scaffolds or from dissociation of scaffold–scaffold interactions. Interestingly, single-molecule tracking experiments could be the first technique to gain access to these dissociation rate constants. Gel filtration experiments have measured a high affinity of the glycine receptor for gephyrin [52]. However, live-cell experiments suggest a weaker interaction (residence time of 0.5 min) or low (10⁻¹–10⁻² μm² s⁻¹) diffusion rates, respectively. Dwell-time distributions of residency at clusters depended on given receptor–scaffold pairs. This probably reflects the association–dissociation rate of the interaction. The physical characteristics of the diffusion were also different: the movements were Brownian-like between scaffold clusters and were confined when within clusters. Brownian movements are dominated by thermal agitation of molecules and are characterized by a linear dependence of the explored surface versus time. By contrast, confined movements, although also powered by thermal agitation, are more complex and spatially limited by interactions with obstacles of various origins (e.g. scaffold proteins, membrane domains or transmembrane proteins). The reversibility of the association of receptors with clusters could result either from the unbinding of receptors from scaffolds or from dissociation of scaffold–scaffold interactions. Interestingly, single-molecule tracking experiments could be the first technique to gain access to these dissociation rate constants. Gel filtration experiments have measured a high affinity of the glycine receptor for gephyrin [52]. However, live-cell experiments suggest a weaker interaction (residence time of ~1 min) either between receptor and scaffold or between scaffold molecules themselves. New experiments will need to be designed to resolve this discrepancy. Furthermore, scaffold proteins such as gephyrin might have non-uniform properties: gephyrin interactions with receptors can be modulated by collybistin [53], pH [52] or splicing [54,55].

Indeed, scaffold molecules can be associated with receptors outside the synapse and can participate in the regulation of trafficking. This is supported by findings that some postsynaptic proteins involved in the synaptic clustering of NMDA and/or AMPA glutamate receptors, such as PSD-95 [56], stargazin [57,58], synapse-associated protein (SAP)102 [59] and AMPA-receptor-binding protein (GRIH/ABP) [60,61], can associate with receptors as they traffic towards or away from the cell surface; this is also the case for gephyrin–glycine receptor association [62].

Observing single receptors yet thinking of the synapse as a whole
Real-time imaging of extrasynaptic receptor movements led us to postulate that receptors could escape synapses through lateral diffusion. However, the size of the latex beads precluded direct visualization of synaptic receptor dynamics. In the search for approaches allowing detection of receptor movements in synapses, single-molecule detection techniques have been developed (Box 1), using either organic dyes or the recently developed inorganic fluorescent semiconductor particles known as quantum dots. Quantitative data were obtained at a single-molecule level for glycine [45], AMPA [31] and NMDA [47] receptors on spinal cord and hippocampal primary neuronal cultures. The diffusion coefficient and receptor behavior in the extrasynaptic membrane were comparable to those obtained using latex beads, as expected from

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<th>Box 1. Single-fluorophore tracking of receptor movements</th>
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<td>In live cells, the ability to detect selectively one or a few molecules is a powerful way to understand the dynamics of cellular organization. Several probes can be used to track receptor movements with an inverse relationship between probe size (which determines the accessibility to synapses) and recording advantages (signal level and photostability). Nonfluorescent latex beads (diameter 200–500 nm) and colloidal gold (diameter 40 nm) used with video-microscopy provided most of our initial knowledge on lateral protein and lipid diffusion. However, the size of these probes precludes access to receptors in the synaptic cleft. The recent development of single-fluorescent-molecule imaging has enabled use of smaller probes. Organic dyes (e.g. cy3, cy5 and rhodamine) were initially used; these are small (1 nm) but photobleach rapidly (&lt;10 s). Semiconductor quantum dots (QDs) are fluorescent probes of intermediate size (~5–10 nm) that are significantly more photostable than conventional fluorophores, and so are suitable for advanced biological imaging. In vitro and in vivo imaging using QDs has recently been demonstrated by several groups, for example in tracking individual surface receptors in the same cellular region for long durations [44,46]. Individual fluorophores bear unique signatures, such as one-step photobleaching, well-defined signals and diffraction-limited spots [68]. Because they are defined point sources that can be imaged on large areas on charge-coupled devices, their localization can be determined with a relative resolution down to the nanometer scale. This precision enables the determination of diffusion coefficients over several orders of magnitude. However, one should keep in mind that seeing a single dye molecule does not necessarily correspond to a single receptor because dyes can be bound to diffusing clusters. The properties of QDs make it possible to record the mobility of individual molecules at the neuronal surface, even in confined cellular compartments. They offer a favorable compromise between small fluorophores and large beads for single-molecule experiments in live cells. Furthermore, QDs can be detected using electron microscopy [45]. The ability to acquire both fluorescence and electron microscopic images with the same probes and labeling procedures provides access to two seemingly irreconcilable types of information: temporal dynamics and high-resolution cellular localization. One should note that this field is still waiting for the ideal photostable small probe. Epitope tagging of receptors using GFP can lead to profound functional perturbations and GFP is a poor fluorophore for single-molecule imaging. Organic dyes are small but photobleach rapidly, and QDs might still be too large to report faithfully receptor movements in confined areas such as the synapse.</td>
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hydrodynamic laws, but important differences were found between mobility of receptor subtypes. For example, NMDA receptors containing NR1 subunits were much less mobile in the extrasynaptic membrane than AMPA receptors containing GluR2 subunits [47].

Two major findings for synaptic receptors were recorded thanks to single dye imaging. First, a surprisingly high proportion of receptors are mobile inside synapses. Second, receptors enter and exit synapses through lateral diffusion (Figure 3a). In synapses, ~30% of glycine receptors and ~50% of AMPA receptors and NMDA receptors were found to be mobile \( (D > 5 \times 10^{-3} \text{ m}^2 \text{s}^{-1}) \). Mobile synaptic receptors displayed confined movement restricted to areas of ~0.1 \( \mu \text{m}^2 \), which corresponds to published values of PSD surface areas. Independent of their intrasynaptic mobility, some receptors escaped the synapse. Receptors moving from synaptic to extrasynaptic localizations and vice versa always transited through perisynaptic space for periods of up to a few minutes. Receptors passing from one synapse to another could be directly observed, and individual receptors explored spaces of between one and two dimensions (as do Peano curves, which can fill a surface) because the trace is linear and the explored space tends to an area for infinite times. The measure of the dimension of this space will enable the influence of neuronal activity on this parameter to be established, and the probability that a given receptor interacts with scaffold proteins to be derived.

Increase in the activity of the neuronal network by KCl-induced depolarization triggered strong increases in AMPA, but not NMDA or glycine, receptor mobility. These changes were detected mainly in the extrasynaptic membrane. By contrast, glycine receptor mobility is increased when excitatory neurotransmission is blocked and this effect is mimicked by buffering intracellular \( \text{Ca}^{2+} \) or blocking the voltage-dependent \( \text{Ca}^{2+} \) channel [63]. These diffusion behaviors could provide the basis for the homeostatically regulated balance between excitation and inhibition and consequently for the activity-dependent synaptic plastic modifications involving groups of synapses.

The molecular mechanisms for the regulation of receptor diffusion are still not identified, although local \( \text{Ca}^{2+} \) increases reduce AMPA receptor mobility [50]. This might be due to regulation of scaffold–receptor interactions or modification of the submembranous cytoskeleton organization. Such a local effect is opposite to that provoked by global neuronal activity. Therefore, AMPA receptor mobility might be differentially regulated by \( \text{Ca}^{2+} \) transients of different origins.

Revisiting receptor stabilization in the light of receptor movements
There is an apparent contradiction between the continuous receptor movements and the apparent stability of synapses [19]. This arises from the difference between the concept of stabilization and that of local concentration of receptors. Images obtained using classical immunocytochemistry reveal a patchy distribution for many receptors, with accumulation at synapses. Actually, this approach generates a snapshot of the statistical distribution of receptors at a given time, indicating that diffusing receptors spend most of their life at synapses. From a thermodynamic point of view, concentration could be achieved using little energy. The observation that receptors are mobile at relatively high rates within synapses prompted us to revisit the notion that synaptic stabilization of receptors results only from interactions with scaffolding proteins (Figure 3b). Other factors could participate in organization of the PSD, such as obstacles acting as corrals and pickets, and weak molecular interactions acting as steric hinderers and attractive potentials, respectively [64,65]. Corrals are formed by the submembranous cytoskeleton [66] and pickets are all transmembrane proteins. Another important structuring element could be lipid organization, because shells of lipids around receptors could slow down their movements in crowded environments such as the PSD. Therefore, we postulate that the confinement of receptors at synapses results from a variety of contributions to the restriction of movements. Each of these contributions could be regulated by specific cell biology mechanisms. More precisely, variation in the number of scaffolding molecules, such as those observed during LTP [19,20], would increase the number of transient interaction sites, whereas changes in transmembrane adhesion molecules [67] would regulate the number of pickets and corrals. Specific and global modulations could synergize to regulate mean receptor numbers by modifying inward and outward fluxes, in addition to the equilibrium set point.

Concluding remarks
Because receptors diffuse in the plasma membrane, in the same way that particles do in a two-dimensional field, they could be transiently trapped at specific loci corresponding to postsynaptic densities. New receptors could pop into or disappear from the plasma membrane by exocytosis and endocytosis, respectively. Another characteristic of the neuronal membrane is that the processes of diffusion, trapping and variation in receptor numbers could be regulated by ‘biological processes’ and could account for learning, memorizing and forgetting. We propose that the plasma membrane can be analyzed globally using a formalism derived from statistical mechanics. This global analysis will require the simultaneous (multicolor) detection and tracking at single-molecule levels of various molecular species on the plasma membrane of identified neurons. This technical target is now reachable. This could open new routes towards understanding not only the dynamic equilibrium accounting for receptor number at synapses, but also the mechanisms underlying the excitation–inhibition balance during modifications induced by so-called plasticity within neuronal networks.

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