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Functional organization of postsynaptic glutamate receptors

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ABSTRACT

Glutamate receptors are the most abundant excitatory neurotransmitter receptors in the brain, responsible for mediating the vast majority of excitatory transmission in neuronal networks. The AMPA- and NMDA-type ionotropic glutamate receptors (iGluRs) are ligand-gated ion channels that mediate the fast synaptic responses, while metabotropic glutamate receptors (mGluRs) are coupled to downstream signaling cascades that act on much slower timescales. These functionally distinct receptor sub-types are co-expressed at individual synapses, allowing for the precise temporal modulation of postsynaptic excitability and plasticity. Intriguingly, these receptors are differentially distributed with respect to the presynaptic release site. While iGluRs are enriched in the core of the synapse directly opposing the release site, mGluRs reside preferentially at the border of the synapse. As such, to understand the differential contribution of these receptors to synaptic transmission, it is important to not only consider their signaling properties, but also the mechanisms that control the spatial segregation of these receptor types within synapses. In this review, we will focus on the mechanisms that control the organization of glutamate receptors at the postsynaptic membrane with respect to the release site, and discuss how this organization could regulate synapse physiology.

1. Introduction

Synapses are the fundamental elements of neuronal networks that enable the processing, encoding, and retrieval of information in the brain, and pathological disruptions in synapse structure are broadly held to underlie the development of neurological disorders such as autism and schizophrenia (Volk et al., 2015). To maintain and adjust the efficiency of synaptic signaling, synapses are built from a broad array of components that assemble into large macromolecular machineries. At the presynaptic terminal, action potentials trigger the fast release of synaptic vesicles. Synaptic vesicles are docked at the active zone and primed for exocytosis by protein complexes containing e.g. Rab3-interacting molecules (RIM) and soluble N-ethylmaleimide-sensitive factor activating protein receptors (SNARE) (Sudhof, 2012). The release of glutamate is closely aligned with the postsynaptic receptors that are stably anchored in the opposing postsynaptic density (PSD), a complex molecular machine containing a plethora of scaffolding proteins and signaling molecules (Okabe, 2007; Sheng and Hoogenraad, 2007). How are these molecular complexes organized and precisely positioned to sustain synaptic transmission? In this review we will focus particularly on the functional distribution of glutamate receptors at the postsynaptic membrane.

2. Functional organization of postsynaptic glutamate receptors

2.1. Impact of glutamate receptor distribution on probability of receptor activation

At excitatory synapses, the postsynaptic effects of glutamate are mediated by different types of glutamate receptors; the ionotropic glutamate receptors (iGluRs) comprising AMPA- and NMDA- and kainate-type receptors, and the metabotropic glutamate receptors (mGluRs). The principal iGluRs, the AMPA and NMDA-type receptors act on millisecond timescales to mediate the majority of fast, basal synaptic transmission. In contrast, the postsynaptic group I mGluRs, i.e. mGluR1 and mGluR5, respond much slower and have much longer-lasting physiological effects. Intriguingly, these functionally distinct receptor types are spatially segregated with respect to the presynaptic release site. While AMPA and NMDA receptors are highly enriched in the core of the PSD opposing the presynaptic release site, mGluRs are preferentially enriched in the perisynaptic domain, much further away from the vesicle release site, and seem to be largely excluded from the PSD (Baude et al., 1993; Lujan et al., 1996; Nusser et al., 1994) (Fig. 1A). We define the perisynaptic domain as an annular ring of 100–200 nm surrounding the PSD, whereas the extrasynaptic domain is everything beyond the perisynaptic domain, and thus starts 100–200 nm away from the edge of the PSD (Fig. 1B).

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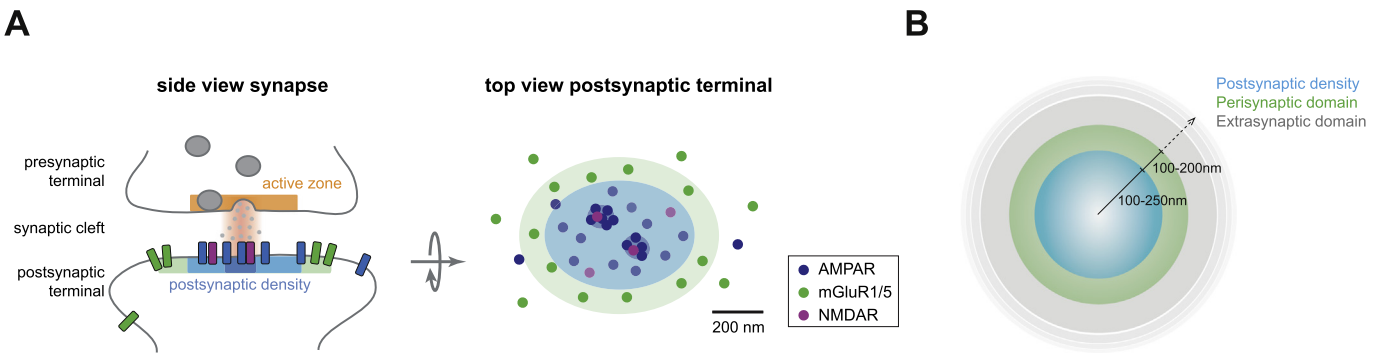

Fig. 1. Subsynaptic segregation of glutamate receptor types at the postsynaptic membrane.
(**A**) Side view of an excitatory synapse with an active zone (orange) at the presynaptic terminal and postsynaptic density (PSD) (blue), and perisynaptic domain (green) at the postsynaptic terminal (left). A single release event of glutamate is predicted to create a subsynaptic hotspot of maximally activated postsynaptic glutamate receptors (dark blue shaded area) aligned with the presynaptic vesicle release site. Top view of the lateral patterning of the postsynaptic membrane with a central PSD (blue) containing AMPA- (dark blue) and NMDA-type (pink) receptors, and a surrounding perisynaptic domain (green) enriched in mGluR1/5 (dark green) (right). Additionally, PSD components, most notably AMPARs, are organized in ~1–3 distinct nanodomains per synapse (dark blue shaded area).
(**B**) Top view of an excitatory postsynapse to make a clear distinction between the PSD, on average 500–1000 nm in diameter, the perisynaptic domain, an annulus of 100–200 nm surrounding the PSD, and the extrasynaptic domain, everything beyond the perisynaptic domain.

The spatial segregation of receptor types has important functional implications as the distinct localization with respect to the presynaptic release site is predicted to greatly impact the activation kinetics of these receptors types. As has been extensively investigated by numerous computational models that incorporate realistic features of glutamate release and synapse geometry single release events produce a very steep peak in synaptic cleft glutamate concentration, restricted to a small area (< 100 nm) for only a brief period of time (~100 µs) (Boucher et al., 2010; Franks et al., 2003; Raghavachari and Lisman, 2004; Uteshev and Pennefather, 1996; Xie et al., 1997; Xu-Friedman and Regehr, 2004). Importantly, the affinity of AMPARs for glutamate is relatively low and the number of glutamate molecules bound to AMPAR subunits determines the open probability of the receptor (Rosenmund et al., 1998). Initially it was thought that receptor activation requires binding of at least two glutamate molecules, however recently it was proposed that in the presence of auxiliary subunits binding of a single glutamate molecule might be sufficient for receptor activation (Coombs et al., 2017; Greger et al., 2017). However, binding of a single glutamate molecule was also shown to be sufficient to desensitize AMPARs (Robert and Howe, 2003), and although the rate of AMPAR desensitization upon binding of a single glutamate molecule is similar when bound to two to four glutamate molecules, the rate of glutamate dissociation is predicted to be slower with at least two glutamate molecules bound (Robert and Howe, 2003). As a result of these biophysical properties, computational models predict that the probability of AMPAR opening is highest near vesicle release sites, producing local hotspots (< 0.03 μm^2) of maximally activated AMPARs that cover only a fraction of the total PSD area (~25% of an average PSD in a CA1 synapse) (Franks et al., 2003; Raghavachari and Lisman, 2004). Importantly, this suggests that not the absolute number, but the density of AMPARs with respect to the presynaptic release site determines the size of the synaptic response. Similarly, although to a lesser extent, the activation probability of NMDARs is also location-dependent. Even though NMDARs have a higher affinity for glutamate and desensitize slower than AMPARs (Erreger et al., 2005), the slow binding rate puts a considerable limit on the opening probability of NMDARs during the short-lived glutamate peak. This is particularly significant for GluN2B-containing NMDARs that are three times more likely to become activated when directly opposing the release site than when displaced > 200 nm. In contrast, the activation probability of GluN2A-containing receptors falls below 50% only when displaced > 300 nm from the release site (Santucci and Raghavachari, 2008). Indeed, receptor non-saturation has been demonstrated experimentally at different types of synapses, where increasing presynaptic release or focal application of exogenous glutamate resulted in larger amplitude responses (Liu et al., 1999; McAllister and Stevens, 2000; Pankratov and Krishtal, 2003).

Even further displaced from the release site are the mGluRs, located at the perisynaptic domain surrounding the PSD, strongly constraining the activation probability of these receptors. The binding affinity of group I mGluRs for glutamate is comparable to AMPARs as measured in heterologous systems (Conn and Pin, 1997; Traynelis et al., 2010), and although one glutamate molecule is sufficient to activate mGluR5 dimers, occupation of both subunits is required for optimal activation (Kniazeff et al., 2004; Niswender and Conn, 2010). Thus, these biophysical properties predict that the low concentration of glutamate at the periphery of the synapse during single release events limits mGluR activation. Moreover, glutamate transporters co-localizing with mGluRs at the perisynaptic domain (Dehnes et al., 1998; He et al., 2000) compete for the residual glutamate that diffuses out of the synaptic cleft, which further enhances the rapid uptake of glutamate, and thereby virtually eliminating the probability of mGluRs to sense glutamate during single release events (Brasnjo and Otis, 2001). Functionally this would imply that mGluRs only respond when cleft glutamate concentration builds up such that it “spills over” to the perisynaptic domain, for instance during sustained high-frequency synaptic stimulation. Consistently, the activation kinetics of group I mGluRs are very fast (< 10 ms) and the deactivation time is slow (~50 ms) (Marcaggi et al., 2009; Rondard and Pin, 2015). Thus, also the intrinsic kinetic profile of mGluRs predicts that these receptors function as integrators of activity and are sensitive to high-frequency (> 20 Hz) pulses of release (Greget et al., 2011; Marcaggi et al., 2009). Indeed, at cerebellar synapses, trains of stimuli with a minimal frequency of 20 Hz are required to elicit mGluR1-mediated excitatory postsynaptic currents (EPSCs) (Tempia et al., 1998).

Taken together, the nanoscale segregation of glutamate receptor subtypes differentially determines their activation probabilities, providing synapses with a powerful means to encode synaptic activity patterns. In the following, we will present an overview of the literature on the molecular organization of excitatory synapses, focusing in particular on the subsynaptic distribution of glutamate receptors at the postsynaptic membrane, and explore the potential physiological consequences of this organization and mechanisms that could control the entry and distribution of receptors in the synapse.

2.2. Subsynaptic segregation of glutamate receptor types

The activation of the distinct receptor subtypes and their contribution to synaptic transmission is controlled by their lateral distribution