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SYMPOSIUM REVIEW

Modulation of information processing by AMPA receptor auxiliary subunits

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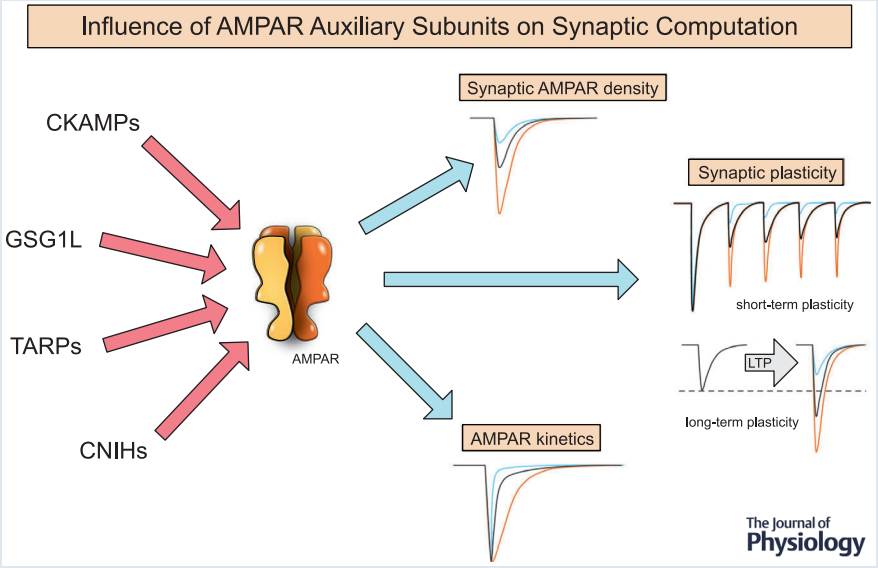

Abstract AMPA-type glutamate receptors (AMPARs) are key molecules of neuronal communication in our brain. The discovery of AMPAR auxiliary subunits, such as proteins of the TARP, CKAMP and CNIH families, fundamentally changed our understanding of how AMPAR function is regulated. Auxiliary subunits control almost all aspects of AMPAR function in the brain. They influence AMPAR assembly, composition, structure, trafficking, subcellular localization and gating. This influence has important implications for synapse function. In the present review, we first discuss how auxiliary subunits affect the strength of synapses by modulating number and localization of AMPARs in synapses as well as their glutamate affinity, conductance and peak open probability. Next we explain how the presence of auxiliary subunits alters temporal precision and integrative properties of synapses by influencing gating kinetics of the receptors. Auxiliary subunits of the TARP and CKAMP family modulate synaptic short-term plasticity by

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increasing anchoring of AMPARs in synapses and by altering their desensitization kinetics. We then describe how auxiliary subunits of the TARP, CKAMP and CNIH families are involved in Hebbian and homeostatic plasticity, which can be explained by their influence on surface trafficking and synaptic targeting. In conclusion, the series of studies covered in this review show that auxiliary subunits play a pivotal role in controlling information processing in the brain by modulating synaptic computation.

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Abstract figure legend AMPA receptor auxiliary subunits: AMPA receptors interact with many different types of proteins. Up to now more than 30 distinct interaction partners have been identified (Schwenk *et al.* 2009, 2012; Engelhardt *et al.* 2010; Shanks *et al.* 2012). However, only a small subset of these interacting proteins belongs to the class of auxiliary subunits. In contrast to other interacting partners such as FRRS1L and ABHD6 that interact with AMPARs exclusively intracellularly (Schwenk *et al.* 2019), auxiliary subunits interact with AMPA receptors on the cell surface, where they modulate their gating and localization (Jacobi & Engelhardt, 2018). The four different protein families that comprise the class of auxiliary subunits are TARPs, CNIHs, CKAMPs and GSG1L. Over the past 20 years, substantial progress has been made in the understanding of how auxiliary subunits interact with AMPA receptors and what the functional consequences of this interaction are. Very recently, for example, the atomic structure of AMPA receptors in complex with TARP γ-8 or CNIH-2 has been resolved (Herguedas *et al.* 2019; Nakagawa, 2019; reviewed in Kamalova & Nakagawa, 2020). Table 1 provides an overview of the main effects of the different AMPA receptor auxiliary subunits.

Introduction

Synaptic transmission via chemical synapses is the main route of neuronal communication and forms the backbone of information processing in the central nervous system. Plastic changes in strength and mode of single synapses alter the way information is integrated and computed in our brain. Fast excitatory synaptic transmission in the central nervous system is mostly mediated by AMPA-type glutamate receptors (AMPA receptors). Their central position in excitatory synapses makes these receptors key targets for the regulation of excitatory synaptic communication. Consequently, alteration in neuronal communication is often mediated by a change in number and function of AMPA receptors.

Structurally, AMPA receptors are heterotetramers that assemble from different combinations of the four AMPA receptor subunits GluA1–GluA4 (AMPA-type glutamate receptor subunit 1–4) (Traynelis *et al.* 2010). The combination of the subunits in the final receptor determines its basic electrophysiological parameters. Moreover, AMPA receptors are embedded into networks of interacting proteins several of which strongly impact AMPA receptor function (Schwenk *et al.* 2009 (CNIHs), 2012 (CNIHs, TARPs, GSG1L); Engelhardt *et al.* 2010 (CKAMP44); Shanks *et al.* 2012 (GSG1L); Greger *et al.* 2017 (TARPs)). The importance of these auxiliary subunits becomes evident if one looks at the broad variety of AMPA receptor-mediated currents in various neuron types in the brain. These currents only partially resemble the ones from heterologous expressed receptors. This discrepancy can be explained by the interaction of auxiliary subunits with AMPA receptors in the brain. In fact, we know today that AMPA receptor function depends to a large extent on the interaction with auxiliary subunits. They influence AMPA receptor trafficking to the cell surface, subcellular localization and gating of the receptors (see Table 1).

Currently, the group of auxiliary subunits of AMPA receptors includes the families of TARPs (transmembrane AMPA receptor regulatory proteins), CNIHs (cornichon homolog proteins), CKAMPs (cysteine-knot AMPA receptor modulating proteins; aka Shisas) and GSG1L (germ cell-specific gene 1 like protein) (Figure 1, Table 1). Auxiliary subunits differ in their influence on AMPA receptor function and, additionally, display distinct regional and developmental expression profiles. Interestingly, the expression of some auxiliary subunits is activity dependent. This indicates an important role of auxiliary subunits in homeostatic synaptic scaling and neuronal adaptation processes. Several recent reviews discuss in detail the influence of auxiliary subunits on AMPA receptor trafficking, assembly, receptor composition, and structure (Eibl & Plested, 2017; Greger *et al.* 2017; Jacobi & Engelhardt, 2017, 2018; Bissen *et al.* 2019; Chen & Gouaux, 2019; Kamalova & Nakagawa, 2021). This review will specifically focus on how AMPA receptor auxiliary subunits influence function and localization of synaptic AMPA receptors and the consequences of this influence on computation of synapses.

Synaptic strength

The strength of a synapse depends on the number of synaptic AMPA receptors (Fig. 2). Throughout the brain,

Table 1. Modulation of AMPA receptors by the different auxiliary subunits

	TARPs						CKAMPs				CNIHs		
	γ-2	γ-3	γ-4	γ-5	γ-7	γ-8	39	44	52	59	CNIH-2	CNIH-3	GSG1L
Trafficking	↑	↑	↑	0	↑	↑	N/A	↑	N/A	N/A	↑	↑	N/A
Synaptic localization	↑	↑	↑	0	↑	↑	N/A	↑	N/A	N/A	↑	N/A	↑
Deactivation rate	↓	↓	↓	↑	↓	↓	0/↓	↓	0/↓	0	↓	↓	↓
Desensitization rate	↓	↓	↓	↑	↓	↓	0/↑	↑	↓/0/↑	0/↑	↓	↓	↓
Recovery from desensitization	↑	N/A	N/A	N/A	N/A	↑	↓	↓	↓/0/↑	0/↓	0	0	↓
Conductance	↑	↑	↑	↑	↑	↑	N/A	↑	N/A	N/A	↑	↑	↓
Glutamate affinity	↑	↑	↑	↓	0	↑	↑	↑	↑	N/A	0	↓	N/A
Long-term plasticity	↑	N/A	N/A	N/A	N/A	↑	N/A	0	N/A	↑	↑	↑	↓
Short-term plasticity	0	0	N/A	N/A	N/A	↑	N/A	↓	↑	0	N/A	N/A	N/A

Opposing effects are probably due to different AMPA receptor subunits or expression systems (e.g. oocytes, HEK293 cells, cultured neurons or acute brain slices). N/A, not available. References: TARPs: Tomita *et al*. 2003; Yamazaki *et al*. 2004; Priel *et al*. 2005; Rouach *et al*. 2005; Cho *et al*. 2007; Milstein *et al*. 2007; Kott *et al*. 2009; Shi *et al*. 2010; Kato *et al*. 2008, 2010; Khodosevich *et al*. 2014; CKAMPs: von Engelhardt *et al*. 2010; Khodosevich *et al*. 2014; Farrow *et al*. 2015; Klaassen *et al*. 2016; Schmitz *et al*. 2017; CNIHs: Schwenk *et al*. 2009; Coombs *et al*. 2012; Kato *et al*. 2010; Herring *et al*. 2013; Boudkkazi *et al*. 2014; GSG1L: Shanks *et al*. 2012; McGee *et al*. 2015; Gu *et al*. 2016; Mao *et al*. 2017.

synaptic AMPA receptor density varies from synapse to synapse and is subject to constant changes. The control of synaptic AMPA receptor number is perhaps one of the most obvious effects of auxiliary subunits. However, the strength of a synapse depends not only on the number of synaptic receptors, but also on their gating properties. Thus, strength of synaptic communication is additionally influenced by glutamate affinity, conductance and peak open probability of AMPA receptors (Fig. 2; Clements, 1996; Kullmann *et al.* 1999; Bredt & Nicoll, 2003; MacGillavry *et al.* 2013). Finally, anchoring of AMPA receptors in subsynaptic nanodomains has been shown to influence synaptic strength (Nair *et al.* 2013). All these receptor properties are differentially influenced and/or controlled by auxiliary subunits, making these proteins key regulators of synaptic strength (Table 1).

The regulation of AMPA receptor density by auxiliary subunits does not depend on a single, uniform mechanism. Some auxiliary subunits affect the trafficking of AMPA receptors to the cell surface, others (and sometimes the same ones) control the anchoring of AMPA receptors at the postsynaptic density. Yet others are thought to affect removal of AMPA receptors from the synapse. To date, the mechanisms of how AMPA receptor auxiliary subunits control receptor trafficking to the cell surface are not fully understood (reviewed in Jacobi & Engelhardt, 2018). Genetic deletion of many auxiliary subunits leads to a significant reduction in surface AMPA receptor levels. This reduction of AMPA receptor number is especially dramatic in TARP γ-2-deficient *stargazer* mice, where the deletion of TARP γ-2 leads to a total loss of surface AMPA receptors on cerebellar granule cells in postnatal day 14 mice (Chen *et al.* 2000). Deletion of other auxiliary subunits shows a less severe impact on AMPA receptor surface levels, presumably due to the high functional and spatial redundancy of large

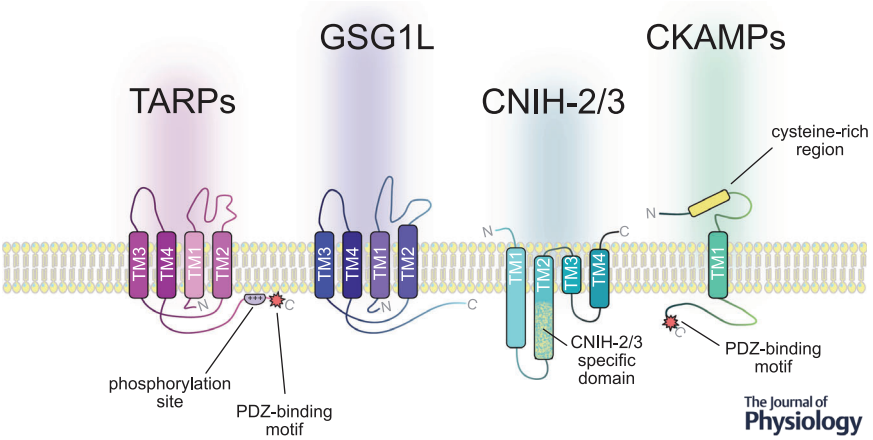

Figure 1. Schematic illustration of the membrane topology of the different families of AMPA receptor auxiliary subunits
Additionally, highlighted are locations of specific domains of the different protein families: the PDZ binding motifs for TARPs and CKAMPs, the C-terminal phosphorylation site of TARPs (that interacts with the cell membrane and influences synaptic anchoring) and the characteristic region of CKAMPs (cysteine-rich region) and CNIH-2/3 (adapted from Monyer & von Engelhardt, 2015 and Kamalova & Nakagawa, 2021).

groups of auxiliary subunits. Hence, deletion of CKAMP44 or TARP γ-8 reduces somatic AMPA receptor currents by approximately 50% in dentate gyrus granule cells. However, the deletion of both auxiliary subunits reduces somatic AMPA receptor currents to approximately 8% (Khodosevich *et al.* 2014). Based on the numbers, the deletion of both subunits seems to be additive. In contrast, in cerebellar Golgi cells synaptic AMPA receptor number is not affected by deletion of TARP γ-2 or TARP γ-3 alone, but is virtually absent in TARP γ-2/γ-3 double knockout mice (estimated from synaptic current amplitudes). This suggests that the two auxiliary subunits are functionally redundant and can compensate for the loss of the other auxiliary subunit (Menuz *et al.* 2008). On the other hand, TARP γ-3 is not expressed in cerebellar granule cells (Tomita *et al.* 2003; Fukaya *et al.* 2005), which explains why it cannot compensate for the loss of TARP γ-2 in this cell type. Interestingly, cerebellar granule cells express TARP γ-7. Knockdown of TARP γ-7 in *stargazer* mice rescues synaptic currents, suggesting that TARP γ-7 prevents synaptic localization of AMPA receptors in the absence of TARP γ-2 (Bats *et al.* 2012). Hence, the effect of the genetic deletion of an AMPA receptor auxiliary subunit depends on the presence of other functionally redundant subunits.

The amplitude of AMPA receptor-mediated currents depends not only on the number of postsynaptic receptors, but also on their affinity to glutamate. AMPA receptors show a relatively low glutamate affinity compared to other glutamate receptors, especially the NMDA receptor-type (Liu *et al.* 1999). Peak synaptic glutamate concentration has been estimated to be in the millimolar range (Rusakov *et al.* 1999; Jonas, 2000). However, peak glutamate concentration rapidly decreases with increasing distance from the presynaptic release site. Simulations and experimental data show that synaptic glutamate concentration is non-saturating, i.e. results in the opening of only a fraction of the postsynaptic AMPA receptors (Liu *et al.* 1999; Rusakov *et al.* 1999; Jonas, 2000; McAllister & Stevens, 2000; Wu *et al.* 2007). Consequently, synaptic strength should depend on glutamate affinity of AMPA receptors. As a corollary, one would assume that auxiliary subunits may influence synaptic strength not only by controlling the number of synaptic AMPA receptors, but also by modulating their glutamate affinity. Several auxiliary subunits of the CKAMP-, CNIH- and TARP-families increase glutamate affinity (Yamazaki *et al.* 2004; Tomita *et al.* 2005*a*; Coombs *et al.* 2012; Khodosevich *et al.* 2014; Farrow *et al.* 2015). An exception is TARP γ-5, which decreases glutamate affinity of GluA2-containing AMPA receptors (Kato *et al.* 2008). Although there is no direct experimental evidence, it is therefore likely that the change in synaptic strength in mice with genetic deletion of auxiliary subunits results not only from an alteration in AMPA receptor number but also from a change in glutamate affinity (Rouach *et al.* 2005; Tomita *et al.* 2005*a*; Menuz *et al.* 2008; Coombs *et al.* 2012; Herring *et al.* 2013; Khodosevich *et al.* 2014; Chen *et al.* 2018).

The strong decline of the glutamate concentration with growing distance from the vesicle release site explains the relevance of the precise subsynaptic position of AMPA receptors for synaptic strength. In fact, AMPA receptors do not distribute uniformly in the synapse, but cluster in nanodomains (Masugi-Tokita *et al.* 2007; MacGillavry *et al.* 2013). Interaction of AMPA receptors

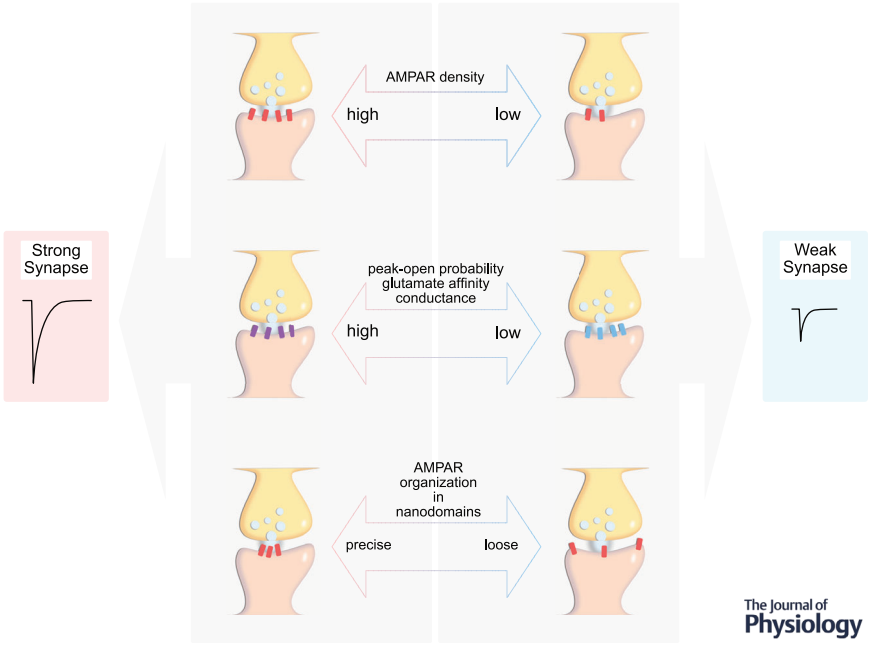

Figure 2. Schematic overview of the influence of AMPA receptor density, gating and postsynaptic organization on synaptic strength
Top, synaptic strength correlates with the number of synaptic AMPA receptors. Middle, synaptic strength depends on peak-open probability, glutamate affinity and conductance of synaptic AMPA receptors. Bottom, postsynaptic AMPA receptor organization is relevant for synaptic strength. Precise localization of AMPA receptors opposite to presynaptic release sites (in so-called nanocolumns) increases synaptic strength, while a more random postsynaptic distribution of AMPA receptors decreases synaptic strength.

with membrane-associated guanylate kinases (MAGUKs) such as PSD95 explains low diffusion rates and hence long dwell times of AMPA receptors in nanodomains (Nair *et al.* 2013). In addition, the N-terminal domain is important for synaptic localization of AMPA receptors (Díaz-Alonso *et al.* 2017; Watson *et al.* 2017). Importantly, the nanodomains are in close proximity with presynaptic vesicle release sites (Tang *et al.* 2016), a structural organization that is most likely mediated by trans-synaptic protein-protein interaction, e.g. between Neuroligin and Neurexin. This alignment of a postsynaptic nanodomain with a presynaptic release site in, so called, nanocolumns ensures high glutamate concentration at the postsynaptic site of AMPA receptor anchoring. Consistently, disruption of nanocolumns by expression of a truncated form of NLG1 reduces synaptic strength (Haas *et al.* 2018). Auxiliary subunits of the CKAMP and TARP families interact with MAGUKs, and in particular with PSD95 (Dakoji *et al.* 2003; Khodosevich *et al.* 2014; Klaassen *et al.* 2016; Schmitz *et al.* 2017). CKAMPs and TARPs therefore increase synaptic strength not only by augmenting synaptic number of AMPA receptors but most likely also by anchoring AMPA receptors in nanodomains in close vicinity of presynaptic vesicle release sites.

Finally, the strength of a synapse depends also on the conductance and peak open probability of its receptors. Most auxiliary subunits increase AMPA receptor conductance and/or peak open probability (Tomita *et al.* 2005*a*; Cho *et al.* 2007; Schwenk *et al.* 2009; Pierce & Niu, 2019). One exception is GSG1L, which decreases synaptic strength in cerebellar and hippocampal neurons, presumably by decreasing the synaptic AMPA receptor density and channel conductance of calcium permeable receptors (McGee *et al.* 2015; Gu *et al.* 2016; Mao *et al.* 2017).

AMPA receptor kinetics

The computation of excitatory synapses depends not only on the peak size of the depolarizing current but also on its shape. Hence, rise time, deactivation and desensitization kinetics of synaptic AMPA receptors determine the charge transfer and timing of synaptic currents and therefore directly affect synaptic communication. Core subunit composition of AMPA receptors (i.e. GluA1-4, flip/flop) determines gating kinetics (Mosbacher *et al.* 1994; Traynelis *et al.* 2010). However, especially deactivation and desensitization rates of AMPA receptors are more strongly affected by the presence of auxiliary subunits. Most known auxiliary subunits decrease the deactivation rate of AMPA receptors, with the exception of TARP γ-5, which increases the deactivation rate. The desensitization rate and/or the steady-state desensitization of AMPA receptors is decreased by TARPs and CNIHs but increased by CKAMPs and GSG1L (Menuz *et al.* 2008; Schwenk *et al.* 2009, 2012; Shanks *et al.* 2012; Straub & Tomita, 2012; Boudkkazi *et al.* 2014; Khodosevich *et al.* 2014). The deactivation time constants of heterologously expressed AMPA receptors without auxiliary subunits are in the range of 0.7 ms (homomeric GluA2o) and 1.3 ms (homomeric GluA1o), i.e. a difference of 600 μs. In contrast, incorporation of TARP γ-8 or CNIH-2 into AMPA receptors increases the deactivation time constant of homomeric GluA1 receptors to *ca* 5 ms and 9 ms, respectively (Kato *et al.* 2010). Similarly, desensitization time constants are several-fold larger in TARP γ-8 or CNIH-2-containing GluA1 receptors compared to pure homomeric GluA1 receptors (Kato *et al.* 2010). Deactivation and desensitization time constants of AMPA receptors are, in most neurons, considerably slower than those of heterologously expressed receptors. For example, principal cells of the hippocampus display deactivation time constants in the range of 2.3 ms (dentate gyrus) and 3 ms (CA1, Colquhoun *et al.* 1992). The most likely explanation for these slow kinetics is the presence of AMPA receptor complexes that contain auxiliary subunits. Indeed, genetic deletion of TARP γ-8, CKAMP44, CKAMP52, GSG1L and CNIH-2 and 3 decreases deactivation time constants of AMPA receptors in CA1 neurons and dentate gyrus granule cells (Rouach *et al.* 2005; Herring *et al.* 2013; Boudkkazi *et al.* 2014; Khodosevich *et al.* 2014; Gu *et al.* 2016; Klaassen *et al.* 2016). Importantly, the magnitude of the influence of auxiliary subunits on gating kinetics strongly depends on the AMPA receptor composition and presence of the flip/flop cassette (Turetsky *et al.* 2005; Tomita *et al.* 2005*a*, 2007; Kato *et al.* 2007, 2010; Kott *et al.* 2007; Morimoto-Tomita *et al.* 2009; Dawe *et al.* 2019)

Experiments with fast application of glutamate onto patches of neurons therefore indeed showed that auxiliary subunits influence gating properties of AMPA receptors in the brain, such as deactivation and desensitization. In most neurons, decays of synaptic currents are mainly dictated by deactivation kinetics of AMPA receptors. This suggests that auxiliary subunits shape decays of synaptic currents. There are a few neuron types that express AMPA receptors with gating kinetics similar to those of homomeric AMPA receptors. Particularly fast deactivation (0.5 ms) has been observed for neurons of the auditory system (Raman *et al.* 1994; Raman & Trussell, 1995). It is likely that AMPA receptors with such fast kinetics contain few auxiliary subunits that slow deactivation such as TARPs or CNIHs. Importantly, decay time constants of synaptic currents are also extremely fast in auditory neurons ($<$1 ms). Axosomatic synapses and short membrane time constants ensure little filtering of synaptic currents and explain negligible temporal summation of auditory inputs (Rothman *et al.* 1993; Raman *et al.* 1994). Several auditory neurons form giant synapses with a high number of

AMPA receptors. The fast kinetics and large amplitude of AMPA receptor-mediated currents in auditory neurons are crucial for conveying temporal information with high fidelity (Rothman *et al.* 1993). Very fast EPSC decays were observed additionally in amacrine, basket and stellate cells (Geiger *et al.* 1997; Crowley *et al.* 2007; Osswald *et al.* 2007), suggesting that in these neurons AMPA receptor auxiliary subunits are also not strongly expressed or exert only a small influence on EPSC decays.

However, compared to the extremely fast kinetics in the aforementioned cells, AMPA receptor decay kinetics are considerably slower in most synapses. For example, AMPA receptor decay rates are around 2–7 ms in hippocampal synapses (Geiger *et al.* 1995; McGee *et al.* 2015; Klaassen *et al.* 2016; Schmitz *et al.* 2017). Consistent with the hypothesis that slow decay kinetics depend on the influence of auxiliary subunits, the deletion of GSG1L, CKAMP52 or CKAMP59 decreases decay rates in these synapses (McGee *et al.* 2015; Klaassen *et al.* 2016; Schmitz *et al.* 2017). Auxiliary subunits therefore alter computational properties of synapses by influencing decay kinetics. Synapses of hilar mossy cells display comparably slow decay kinetics (*ca* 12 ms), which is explained by a high expression of CNIH-2 in this cell type (Boudkkazi *et al.* 2014). The slow kinetics make these synapses less suitable for transmission of information with high temporal precision, but ideal for the integration of information.

AMPA receptor Ca^{2+} permeability

Ca^{2+} permeability and conductance of AMPA receptors depends on their subunit composition. Thus, GluA2-containing AMPA receptors are Ca^{2+} impermeable, and GluA2-lacking AMPA receptors are Ca^{2+} permeable. Moreover, the presence of the subunit GluA2 decreases the conductance (Verdoorn *et al.* 1991; Burnashev *et al.* 1992). Consequently, the composition of AMPA receptors directly affects the computation of synapses.

The regulation of AMPA receptor composition by auxiliary subunits is mainly based on the specific interaction with certain receptor subunits and takes place on different functional levels. These different levels of regulation on one hand, and the presence of more than one auxiliary subunit per cell on the other, leads to a complex and sometimes not uniform effect of auxiliary subunits on receptor composition throughout the brain. TARP γ-2, for example, specifically protects GluA1-containing receptors from lysosomal degradation and thereby alters receptor composition in CA1 neurons (Kessels & Malinow, 2009). On the other hand, enhancement of cytoplasmic polyamine block of AMPA receptors in stellate cells of TARP γ-2 knockout mice or in Golgi cells of TARP γ-2/γ-3 knockout mice suggests that TARP γ-2 and/or γ-3 increase the number of GluA2-containing AMPA receptors in these cell types (Menuz *et al.* 2008; Bats *et al.* 2012). However, since TARPs themselves attenuate the polyamine block (Soto *et al.* 2014; Brown *et al.* 2017), it is also reasonable that the change in polyamine block in TARP γ-2/γ-3 knockout mice is not only due to a decrease in GluA2-containing AMPA receptors, but also due to the loss of the direct influence of TARPs on polyamine block. TARP γ-8 controls, together with the auxiliary subunits CNIH-2 and CNIH-3, the surface levels of GluA1-containing receptors in CA1 pyramidal neurons. The presence of TARP γ-8 may prevent the interaction of CNIH-2/-3 with subunits other than GluA1 and, thus, selectively promotes the trafficking of these receptors to the cell surface (Herring *et al.* 2013; but see also Boudkkazi *et al.* 2014). Yet another mechanism of the regulation of subunit composition by auxiliary subunits has been described by McGee and colleagues (McGee *et al.* 2015). The auxiliary subunit GSG1L specifically supresses currents of calcium permeable AMPA receptors by decreasing their Ca^{2+}-permeability and conductance. Thus, in contrast to the other auxiliary subunits, GSG1L directly supresses the function of certain receptors, rather than promoting it.

Short-term plasticity

The main determinant for synaptic short-term plasticity in many synapses is the release probability of presynaptic vesicles. However, in synapses that frequently have two consecutive vesicle releases in a short period of time, AMPA receptor desensitization is relevant for short-term plasticity in addition to the presynaptic factors. High release probability, but also spill-over of glutamate from one release site to a neighbouring release site and slow diffusion of glutamate out of a synapse favour the influence of AMPA receptor desensitization on short-term plasticity (Blitz *et al.* 2004). Hence, the specific geometry of a synapse and the proximity of neighbouring release sites affects short-term plasticity via the desensitization of AMPA receptors. For example, AMPA receptor desensitization alters short-term plasticity in retinogeniculate synapses of relay neurons in the lateral geniculate nucleus (Chen *et al.* 2002; Hauser *et al.* 2014). Retinogeniculate synapses are very large synapses that contain many release sites (Rafols & Valverde, 1973). This allows spill-over of glutamate from active to non-active release sites. In addition, the geometry of retinogeniculate synapses precludes fast diffusion of glutamate out of the synaptic cleft (Rafols & Valverde, 1973; Budisantoso *et al.* 2012). Hence, presynaptic release of glutamate effectively desensitizes AMPA receptors in active and non-active neighbouring release sites of the same synapse (Budisantoso *et al.* 2012).

Examining the effect of receptor desensitization on short-term plasticity more closely shows that it is especially the time course of the recovery from desensitization of

AMPA receptors that affects synaptic short-term plasticity. AMPA receptor desensitization and the recovery from desensitization are differentially modulated by different auxiliary subunits (Boudkkazi *et al.* 2014; Khodosevich *et al.* 2014; Farrow *et al.* 2015; McGee *et al.* 2015). For example, while heterologously expressed AMPA receptors that contain no auxiliary subunits recover very quickly from desensitization (time constants between 16 and 44 ms for GluA2–4; GluA1i = 151 ms, GluA1o = 105 ms; Kessler *et al.* 2008), the presence of the two auxiliary subunits CKAMP39 and CKAMP44 strongly slows recovery from desensitization. Thus, CKAMP39 and CKAMP44 increase the time constant of recovery from desensitization of AMPA receptors *ca* 10-fold. The time constants from heterologously expressed CKAMP44-containing AMPA receptors is consistent with the comparably slow recovery from desensitization of AMPA receptors found in neurons with high CKAMP44 expression (Khodosevich *et al.* 2014; Chen *et al.* 2018). TARPs on the other hand, decrease the time constant of recovery from desensitization (Priel *et al.* 2005; Khodosevich *et al.* 2014). Importantly, the genetic deletion of CKAMP44 or TARP γ-8 affects short-term plasticity in the hippocampus. Thus, short-term depression is stronger in TARP γ-8 knockout mice and less pronounced in CKAMP44 knockout mice (Khodosevich *et al.* 2014). Short-term plasticity experiments in the presence of cyclothiazide, a potent blocker of AMPA receptor desensitization, proved that the influence of the two proteins on short-term plasticity indeed results from their effect on the rate of recovery from desensitization of AMPA receptors (Khodosevich *et al.* 2014).

AMPA receptor diffusion mitigates the effect of desensitization on short-term plasticity. Thus, desensitized AMPA receptors diffuse out of the synapse and are replaced by non-desensitized AMPA receptors (Heine *et al.* 2008; Constals *et al.* 2015). Auxiliary subunits such as TARPs and CKAMPs reduce AMPA receptor diffusion by anchoring receptors to scaffolding proteins at the postsynaptic density (PSD) (Bats *et al.* 2007; Opazo *et al.* 2010; Sumioka *et al.* 2010; Klaassen *et al.* 2016). Auxiliary subunits should therefore in principle prolong the time that a desensitized AMPA receptor dwells in the synapse. However, synaptic anchoring by auxiliary subunits seems to depend on the conformation of the receptors and is weakened upon AMPA receptor desensitization (Constals *et al.* 2015). Thus, desensitized AMPA receptors show a higher mobility than non-desensitized AMPA receptors. Consequently, desensitized receptors diffuse out of the synapse and can be replaced by non-desensitized receptors. This can be explained by an unbinding of desensitized AMPA receptors from TARPs (Constals *et al.* 2015). The dwell time of AMPA receptors in synapses depends not only intracellular anchoring but also on their N-terminal domain (Díaz-Alonso *et al.* 2017; Watson *et al.* 2017) via which AMPA receptors may interact with extracellular or presynaptic proteins. It remains to be shown whether the N-terminal domain influences short-term plasticity by affecting diffusion of AMPA receptors. In addition, the N-terminal domain is highly mobile (Dawe *et al.* 2019) and it is possible that the agonist induced compression of the N-terminal domain alters synaptic anchoring and diffusion of AMPA receptors.

Klaassen and colleagues showed that auxiliary subunits can also influence short-term plasticity by affecting the decay kinetics of synaptic AMPA receptors (Klaassen *et al.* 2016). Short-term plasticity may be influenced by decay kinetics if firing frequency of presynaptic cells is high, i.e. when the activation of AMPA receptors occurs during the decay phase of a previous activation. CKAMP52 (aka shisa6) reduces the rate of AMPA receptor deactivation. Consistently, genetic deletion renders the decay of synaptic currents in CA1 neurons faster. This explains the decrease in short-term facilitation in CKAMP52 knockout mice when CA1 neurons are stimulated with high frequency of 50 Hz (Klaassen *et al.* 2016).

Short-term plasticity is usually tested in acute brain slices with artificial stimulation protocols. Neuronal firing patterns, but also release probability, glutamate diffusion and reuptake may be different *in vivo*. To understand whether AMPA receptor auxiliary subunits influence synaptic computation also *in vivo*, we recorded firing rates of lateral geniculate nucleus relay neurons in head-fixed non-anaesthetized mice in response to visual stimuli. The magnitude of *On*- and *Off*-responses was increased in CKAMP44 knockout mice compared to wild-type mice. These findings confirmed the data from acute brain slice experiments showing that CKAMP44 influences computation of synapses by affecting short-term depression (Fig. 3). Interestingly, CKAMP44 reduces relay neuron responses by this mechanism despite the fact that it increases the number of synaptic AMPA receptors (Chen *et al.* 2018). The data also imply that the influence of CKAMP44 on relay neuron firing is relevant in particular when presynaptic retinal ganglion cells fire at high frequency (Chen *et al.* 2018).

Long-term plasticity (LTP/LTD)

Long lasting alterations of the strength of synapses are believed to be the foundation of learning and memory. Since the first description of LTP by Bliss and Lomo in 1973, it has become clear that long lasting synaptic plasticity is not uniform, but exists in many different variations (reviewed in Huganir & Nicoll, 2013). A fundamental mechanism underlying LTP and LTD in many synapses is a change in the number of synaptic AMPA receptors. Several AMPA receptor auxiliary subunits including TARP γ-2 and γ-8,

CKAMP59, CNIH-2/-3 and GSG1L influence synaptic long-term plasticity (Rouach *et al.* 2005; Tomita *et al.* 2005*b*; Herring *et al.* 2013; Khodosevich *et al.* 2014; Gu *et al.* 2016; Schmitz *et al.* 2017). This effect of auxiliary subunits on long-term plasticity is perhaps not too surprising, considering their role in the control of trafficking and subcellular localization of AMPA receptors. The mechanisms of how auxiliary subunits influence LTP have been extensively investigated for TARPs. For example, hippocampal LTP depends on phosphorylation of TARP γ-2 (Tomita *et al.* 2005*b*). Hippocampal and cerebellar LTD on the other hand require dephosphorylation of TARP γ-2 (Tomita *et al.* 2005*b*; Nomura *et al.* 2012). Similarly, phosphorylation of TARP γ-8 by CaMKII is needed for expression of LTP in hippocampal neurons (Park *et al.* 2016). Phosphorylation of TARPs initiates diffusion and synaptic trapping of AMPA receptor complexes via interaction with PDZ-domain containing proteins such as PSD95 (Hafner *et al.* 2015). Besides TARP γ-2 and γ-8, the auxiliary subunits CNIH-2/-3 and GSG1L also affect LTP. However, while CNIH-2/-3, like the TARPs, is needed for normal LTP expression, GSG1L seems to suppress LTP (Herring *et al.* 2013; Gu *et al.* 2016).

Homeostatic plasticity

In order to integrate a broad spectrum of synaptic input and, at the same time, maintain a relatively stable output, neurons adjust the strength of their synapses by altering synaptic AMPA receptor density (O'Brien *et al.* 1998; Turrigiano *et al.* 1998). This form of long-term plasticity is termed *homeostatic scaling* and has to be separated from the Hebbian forms of synaptic plasticity that have been described above. However, similarly to Hebbian plasticity, changes in AMPA receptor density are the underlying mechanisms of up- and down-scaling of synapses. Additionally, other processes, such as alterations in the subunit composition of synaptic AMPA receptors and their phosphorylation pattern play a role during homeostatic scaling (Siddoway *et al.* 2013; Soares *et al.* 2013; Diering *et al.* 2014; Kim & Ziff, 2014). The influence of auxiliary subunits on AMPA receptor trafficking suggests that they may play a role in homeostatic scaling. Indeed, visual deprivation or TTX treatment increases the expression and phosphorylation of TARP γ-2 in the lateral geniculate nucleus or in cortical cultures, respectively (Louros *et al.* 2014). Importantly, synaptic up-scaling in response to visual deprivation depends on

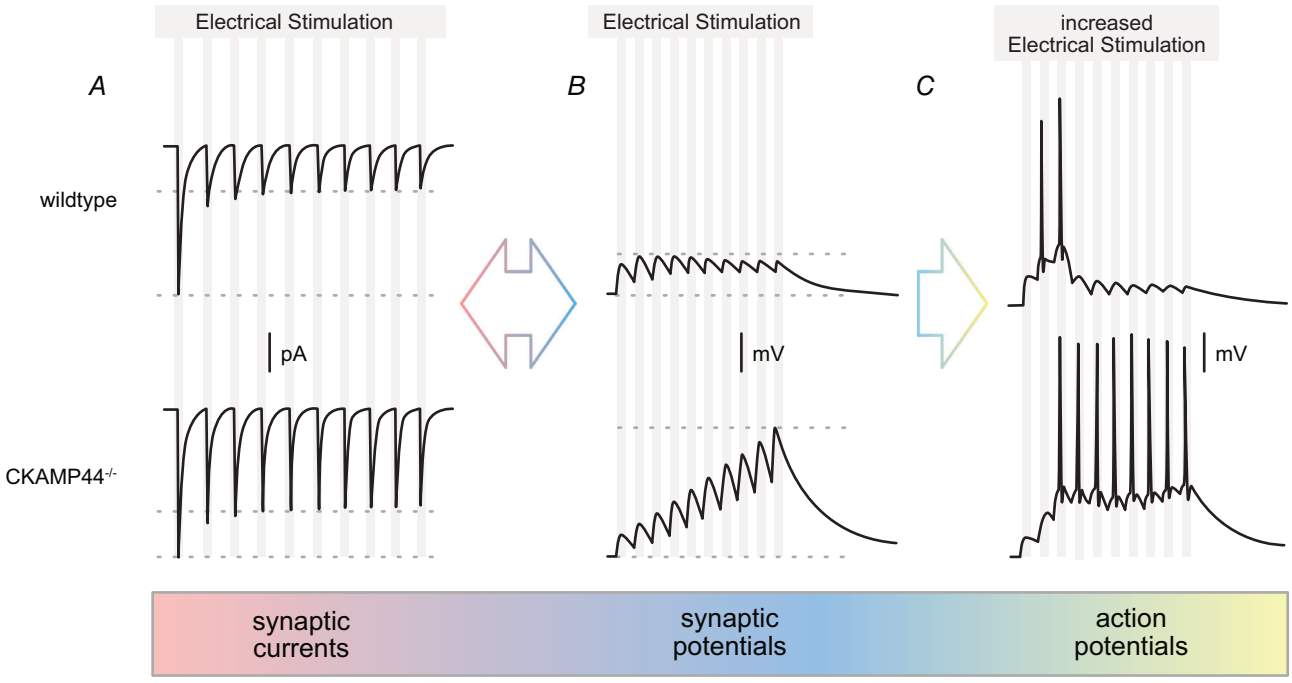

Figure 3. Effect of AMPA receptor auxiliary subunits on neuronal computation by the example of CKAMP44
A, short-term depression of synaptic currents is less strong in retinogeniculate synapses of lateral geniculate relay neurons of CKAMP44$^{-/-}$ mice than in wild-type mice. *B*, the weaker short-term depression in CKAMP44$^{-/-}$ mice explains the augmented postsynaptic depolarization in response to train stimulation of retinogeniculate synapses. *C*, relay neurons fire action potentials when the same stimulus train as in *B* is delivered with stronger stimulation strength. Relay neurons show increased firing probability in response to this stimulus train than relay neurons of wild-type mice. This difference is also explained by the difference in short-term plasticity (adapted from Chen *et al*. 2018).

the phosphorylation of TARP γ-2 (Louros *et al.* 2014). Additionally, dephosphorylation of TARP γ-2 mediates downscaling of cortical synapses (Louros *et al.* 2018). It is not known whether synaptic properties, and in consequence synaptic computation, are altered during homeostatic plasticity due to changes in auxiliary subunit expression.

Conclusion

AMPA receptor auxiliary subunits provide neurons with a versatile tool to adjust their synaptic function according to their computational needs. The composition of AMPA receptor complexes influences EPSC kinetics, and synaptic short-term and long-term plasticity. Changes in the expression of auxiliary subunits in the context of homeostatic plasticity may therefore increase or decrease synaptic strength. In addition, homeostatic changes in AMPA receptor composition could affect how neurons compute excitatory inputs by altering EPSC kinetics, short-term plasticity and long-term plasticity rules. A detailed knowledge of the effects of AMPA receptor auxiliary subunits in physiological but also in pathological conditions is crucial for an understanding of their role in neurological or psychiatric diseases. Genetic linkage analyses suggest that TARP γ-2 and γ-3 may be implicated in familial epilepsy, Alzheimer's disease, schizophrenia and bipolar disorders (Wilson *et al.* 2006; Everett *et al.* 2007; Knight *et al.* 2008; Liu *et al.* 2008; Silberberg *et al.* 2008; Ament *et al.* 2015; Savas *et al.* 2017). This knowledge would also be relevant for the development of novel drugs that target specific AMPA receptor compositions, such as the recently published LY3130481, which efficiently reduces epileptic activity in rodents by blocking specifically TARP γ-8-containing AMPA receptors. Hippocampal and cortical neurons, but not, for example, cerebellar neurons, display high expression levels of TARP γ-8. This may explain why LY3130481 has considerably fewer motor side effects than perampanel, an antiepileptic drug that is an unspecific AMPA receptor antagonist (Kato *et al.* 2016).

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Additional information

Competing interests

The authors declare no financial conflicts of interest.

Author contributions

J.v.E. and E.J. contributed to the conception and design of the work, drafted the work and revised it critically for important intellectual content, approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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