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SYMPOSIUM REVIEW

Role of AMPA receptor desensitization in short term depression – lessons from retinogeniculate synapses

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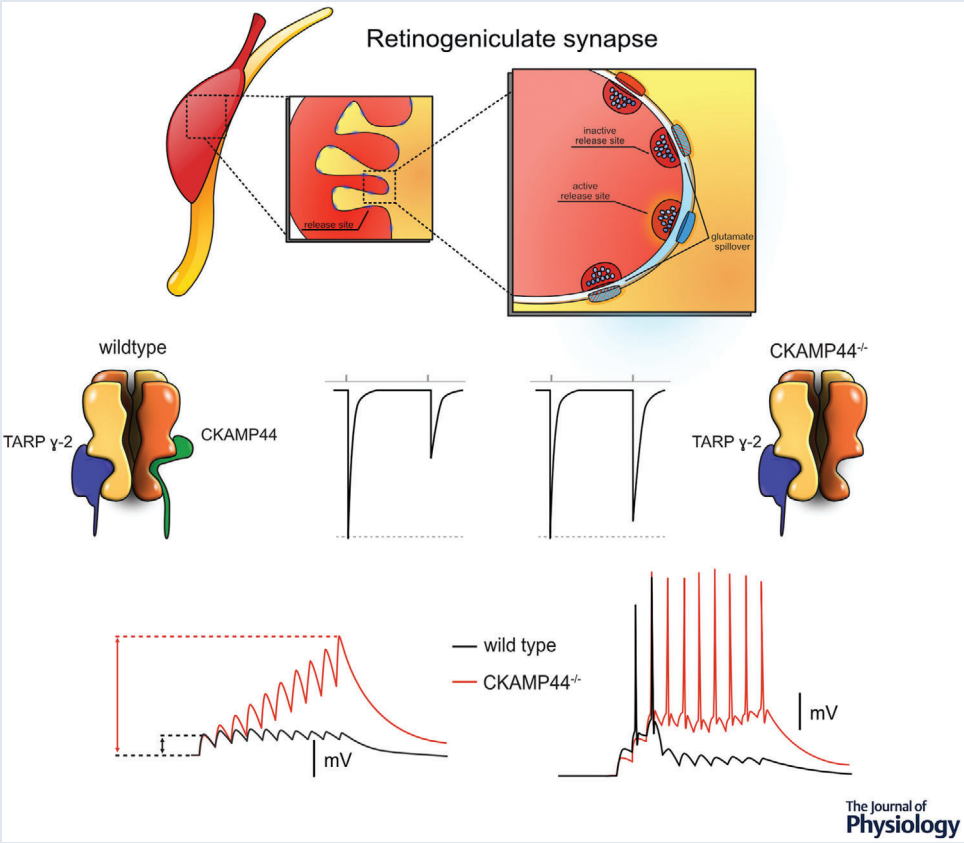

Abstract Repetitive synapse activity induces various forms of short-term plasticity. The role of presynaptic mechanisms such as residual Ca^{2+} and vesicle depletion in short-term facilitation and

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short-term depression is well established. On the other hand, the contribution of postsynaptic mechanisms such as receptor desensitization and saturation to short-term plasticity is less well known and often ignored. In this review, I will describe short-term plasticity in retinogeniculate synapses of relay neurons of the dorsal lateral geniculate nucleus (dLGN) to exemplify the synaptic properties that facilitate the contribution of AMPA receptor desensitization to short-term plasticity. These include high vesicle release probability, glutamate spillover and, importantly, slow recovery from desensitization of AMPA receptors. The latter is strongly regulated by the interaction of AMPA receptors with auxiliary proteins such as CKAMP44. Finally, I discuss the relevance of short-term plasticity in retinogeniculate synapses for the processing of visual information by LGN relay neurons.

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Abstract figure legend Retinogeniculate synapses of the dLGN are large synapses with multiple release sites. Pronounced short-term depression of currents in retinogeniculate synapses results from high release probability and desensitization of AMPA receptors. Spillover of glutamate from active to non-active release sites increases AMPA receptor desensitization. In addition, the depression is long lasting due to the slow recovery from desensitization of AMPA receptors. CKAMP44 is an AMPA receptor auxiliary subunit that decreases the rate of recovery from desensitization. Genetic deletion of CKAMP44 decreases short-term depression (i.e. increase in paired-pulse ratio of currents), and thereby increases relay neuron depolarization and spike probability during activation of retinal inputs to the dLGN.

Introduction

The dLGN of the thalamus is the first relay station for visual information. Relay neurons of the dLGN receive visual information from retinal ganglion cells via retinogeniculate synapses. As the name 'relay neuron' implies, it has long been assumed that the retinal information is simply relayed to the cortex. However, relay neurons of the dLGN transform information that they receive before sending it to the cortex. Passive and active electrophysiological properties of relay neurons, feed-forward and feedback inhibition, modulatory inputs from the cortex and from subcortical regions such as the superior colliculus and the hypothalamus contribute to the shaping of visual information (Guido, 2018). In addition, the specific properties of retinogeniculate synapses play an important role in transformation of inputs. The timing of retinal ganglion action potentials is very important for spike transmission onto dLGN relay neurons. Thus, transmission rate is particularly high for spike frequencies of more than 30 Hz (Mastronarde, 1987; Usrey *et al.* 1998; Carandini *et al.* 2007; Sincich *et al.* 2007; Weyand, 2007; Alitto *et al.* 2011). Retinogeniculate synapses display pronounced short-term depression at these frequencies. This suggests that synaptic short-term plasticity plays a crucial role for input integration of relay neurons (Blitz & Regehr, 2003; Chen *et al.* 2003; Gutig *et al.* 2013).

In this Symposium Review, I will report on the properties that are the basis of short-term depression at retinogeniculate synapses, i.e. the anatomical peculiarities, the specifics of its pre- and postsynaptic function and the composition of AMPA receptors. In addition, I will discuss the relevance of short-term depression in retinogeniculate synapses for processing of visual information in the dLGN. The anatomical organization, the development and the principles of experience-dependent plasticity of the dLGN are not focus of this review but have been recently discussed in several excellent reviews (Cox & Beatty, 2017; Litvina & Chen, 2017; Monavarfeshani *et al.* 2017; Guido, 2018; Bickford, 2019; Liang & Chen, 2020).

Presynaptic and postsynaptic function of retinogeniculate synapses

In most synapses, presynaptic mechanisms shape short-term plasticity. Thus, vesicle depletion in high-release probability synapses causes depression of current amplitudes (Fioravante & Regehr, 2011). In contrast, residual Ca^{2+} explains the increase in release probability and thus short-term facilitation in a low release probability synapse (Fioravante & Regehr, 2011). Retinogeniculate synapses display pronounced short-term depression with paired-pulse ratios of approximately 0.25 (EPSC2/EPSC1) for interstimulus intervals of 10 ms (Turner & Salt, 1998; Chen & Regehr, 2000; Hauser *et al.* 2014; Chen *et al.* 2018, 2019). A

high release probability of 0.7 (Budisantoso *et al.* 2012) explains in part the pronounced short-term depression of retinogeniculate synapses. However, desensitization of postsynaptic AMPA receptors contributes considerably to the short-term depression (Chen *et al.* 2000, Chen *et al.* 2002; Kielland & Heggelund, 2002). Thus, block of AMPA receptor desensitization with cyclothiazide increases the paired-pulse ratio of AMPA receptor-mediated currents (Chen & Regehr, 2000) (Fig. 1). This effect does not result from an influence of cyclothiazide on presynaptic vesicle release probability as cyclothiazide does not affect the paired-pulse ratio of NMDA receptor-mediated currents in this synapse (Chen & Regehr, 2000). In addition, the paired-pulse ratio increases also in the presence of the low affinity competitive antagonist γDGG (Budisantoso *et al.* 2012). AMPA receptors that are blocked by γDGG are prevented from entering the desensitized state such that they can be activated during a subsequent glutamate release (Chanda & Xu-Friedman, 2010). The increase in the paired-pulse ratio in the presence of cyclothiazide or γDGG convincingly demonstrates that AMPA receptor desensitization contributes to short-term depression in retinogeniculate synapses. This is corroborated by the observation that currents that are mediated by NMDA receptors, which show little desensitization, display significantly less short-term depression than AMPA receptor-mediated currents in retinogeniculate synapses (Chen *et al.* 2002).

Relay neurons of the dLGN also receive excitatory input from the cortex via corticogeniculate synapses, which are facilitating in contrast to retinogeniculate synapses. The short-term facilitation results from an increase in vesicle release probability (Granseth & Lindstrom, 2003). AMPA receptor desensitization does not affect short-term plasticity in this synapse (Granseth *et al.* 2002; Granseth & Lindstrom, 2003). This can be explained by the fact that corticogeniculate synapses have a very high failure rate (resting release probability = 0.09) (Granseth & Lindstrom, 2003). Consequently, the likelihood of two consecutive vesicle releases is low (Granseth & Lindstrom, 2003) and only few AMPA receptors will be desensitized at individual synapses when glutamate is released during a second activation of the synapse.

High release probability is one prerequisite for a contribution of AMPA receptor desensitization to short-term depression. It requires two consecutive vesicle releases such that AMPA receptor desensitization can contribute to synaptic depression. I will discuss later the contribution of glutamate spillover from active release sites to non-active release sites. Another important factor is the amount of released glutamate. Decreasing the vesicle release probability by lowering extracellular Ca^{2+} concentration from 2 to 1 mM significantly increases the block of AMPA receptor-mediated EPSCs by the low affinity competitive antagonist γDGG. This suggests that the glutamate concentration in the synaptic cleft correlates with the amount of extracellular Ca^{2+}, which can be explained by multivesicular release at 2 mM extracellular Ca^{2+} (Budisantoso *et al.* 2012). Simulations indicate that the higher glutamate concentration in retinogeniculate synapses with multivesicular release nearly doubles the peak open probability of postsynaptic AMPA receptors (from 0.16 to 0.27). However, this higher glutamate concentration also increases AMPA receptor desensitization and therefore contributes to short-term depression (Budisantoso *et al.* 2012).

AMPA receptors in retinogeniculate synapses

High vesicle release probability is necessary but not sufficient for a relevant contribution of AMPA receptor desensitization to short-term depression. A strong and long-lasting desensitization of AMPA receptors is the other important factor. Cyclothiazide increases the paired-pulse ratio for current pairs with interstimulus intervals of 1 s (Hauser *et al.* 2013). Thus, AMPA receptor desensitization contributes to short-term plasticity for a comparatively long time, which is surprising when considering the fast recovery from desensitization of heterologously expressed AMPA receptors (Kessler *et al.* 2008). AMPA receptors are tetramers composed of different combinations of the four subunits GluA1-4

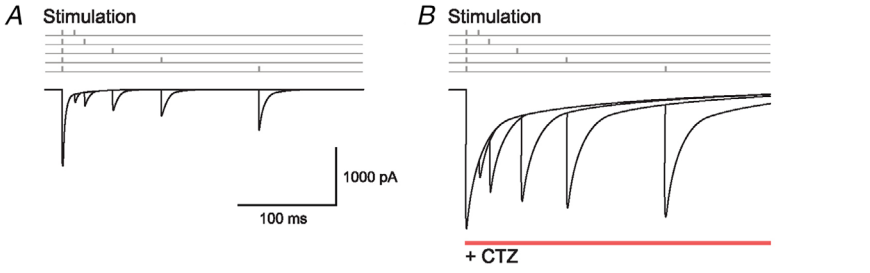

Figure 1. Short-term depression in retinogeniculate synapses
A, EPSCs evoked by two stimulations of retinogeniculate synapses with different interstimulus intervals display pronounced short-term depression. *B*, short-term depression is reduced in the presence of cyclothiazide (CTZ), which blocks AMPA receptor desensitization. (Illustration based on Hauser *et al.* 2013.)

(Traynelis *et al.* 2010). AMPA receptor function depends on subunit composition and the presence of the alternatively spliced flip/flop cassette (Hollmann *et al.* 1991; Lomeli *et al.* 1994; Mosbacher *et al.* 1994). For example, GluA2-lacking AMPA receptors are Ca^{2+} permeable, blocked by intracellular polyamines and have a higher conductance than GluA2-containing AMPA receptors (Verdoorn *et al.* 1991; Burnashev *et al.* 1992). In addition, gating kinetics such as deactivation, desensitization and recovery from desensitization rates depend on AMPA receptor composition (Mosbacher *et al.* 1994; Traynelis *et al.* 2010). Experiments with AMPA receptors expressed in HEK293 cells showed that the different homomeric receptors (GluA1, GluA2, GluA2 and GluA4, flip and flop variants) display very different desensitization and recovery from desensitization rates. Homomeric GluA1i AMPA receptors recover an order of magnitude slower from desensitization than homomeric GluA3i AMPA receptors ($\tau_{recovery}$: 151 ms for GluA1i and 16 ms for GluA3i) (Kessler *et al.* 2008). Native AMPA receptors in the brain are very often not homomers but heteromers, e.g. GluA1/2 and GluA2/3 in hippocampal CA1 neuron (Lu *et al.* 2009). The gating kinetics of heteromeric AMPA receptors are usually in between that of the respective homomers. However, frequently one subunit dominates the gating of the receptor. For example, the rate of recovery from desensitization of GluA1i/GluA2i heteromeric AMPA receptors is much closer to that of GluA2i than of GluA1i homomeric AMPA receptors (Grosskreutz *et al.* 2003).

The exact composition of AMPA receptors in retinogeniculate synapses is unknown. Based on the Allen Brain Atlas, mRNAs of all four GluA subunits are expressed in the dLGN (Lein *et al.* 2007) (Fig. 2). Immunostaining and EM analyses suggest that GluA1 is preferentially found in retinogeniculate synapses, whereas GluA4 is expressed in corticogeniculate synapses (Kielland *et al.* 2009). Considering a comparably high *gria3* mRNA signal in the dLGN (Lein *et al.* 2007), it is likely that GluA3-containing AMPA receptors are also expressed in retinogeniculate synapses. In addition, a significant portion of AMPA receptors in retinogeniculate synapses are GluA2-lacking Ca^{2+}-permeable AMPA receptors as evidenced by partial inward rectification and sensitivity to intracellular spermine and extracellular NASPM of EPSCs (Budisantoso *et al.* 2012; Hauser *et al.* 2014). Ca^{2+}-permeable GluA1-containing AMPARs recover considerably slower from desensitization than heteromeric GluA1/GluA2 AMPARs (Lomeli *et al.* 1994; *Grosskreutz et al.* 2003; Kessler *et al.* 2008). Consistently, the paired pulse ratio of EPSCs in retinogeniculate synapses increased after blocking Ca^{2+}-permeable AMPA receptors with NASPM (Budisantoso *et al.* 2012). In addition, paired-pulse depression was less pronounced in relay neurons of GluA1 knockout mice (Budisantoso *et al.* 2012). Together these findings suggested that GluA1-containing Ca^{2+}-permeable AMPA receptors are among the AMPA receptors in retinogeniculate synapses that recover particularly slowly from desensitization. However, the AMPA receptor-mediated currents of dLGN

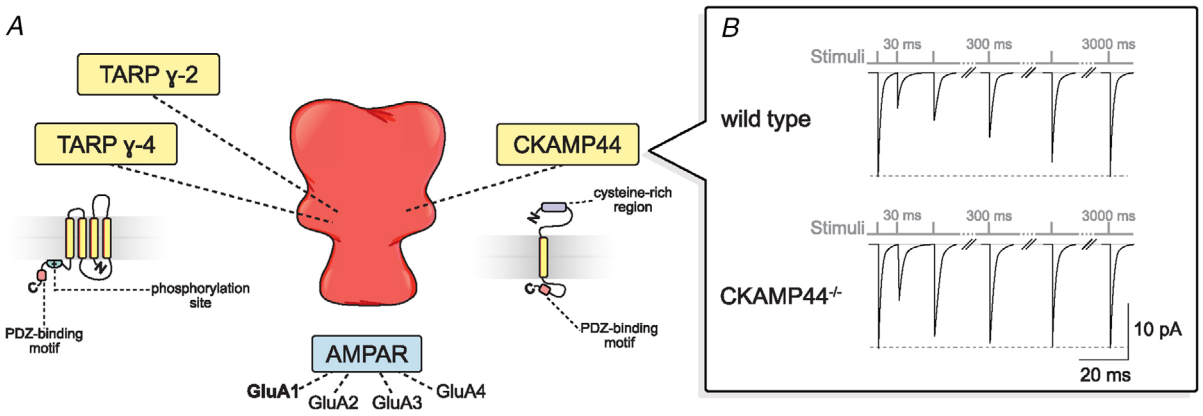

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Figure 2. AMPA receptors in retinogeniculate synapses
A, based on expression and functional analyses, AMPA receptors in the dLGN contain all four GluA subunits, and the auxiliary subunits TARP γ-2, γ-4 and CKAMP44. GluA1 might be more abundant in retinogeniculate synapses than the other GluA subunits. *B*, CKAMP44 affects short-term plasticity in retinogeniculate synapses. Paired-pulse ratios of AMPA receptor-mediated currents in retinogeniculate synapses are increased in relay neurons of CKAMP44$^{-/-}$ mice. This change in short-term depression results from a faster recovery from desensitization of AMPA receptors that do not interact with CKAMP44. (Based on Chen *et al.* 2018.)

relay neurons that we evoked by ultra-fast application of glutamate onto nucleated patches have a $\tau_{recovery}$ of 322 ms (Chen *et al.* 2018). Thus, the recovery from desensitization is considerably slower than the recovery of 'slow' homomeric GluA1i AMPA receptors ($\tau_{recovery}$: 151 ms). This suggested that the function of AMPA receptors in dLGN neurons is modulated by interaction with auxiliary subunits (Fig. 2).

Stargazin (aka TARP γ-2) was the first protein that was identified as an AMPA receptor auxiliary subunit (Chen *et al.* 1999, 2000; Hashimoto *et al.* 1999; Tomita *et al.* 2004; Vandenberghe *et al.* 2005). Subsequently several other auxiliary proteins were found, including other members of the TARP family (TARP γ-3, γ-4, γ-5, γ-7, γ-8), cornichon homologue CNIH2 and 3, the members of the CKAMP family (CKAMP39, 44, 52 and 59; aka shisa 6–9) and GSG1L (Tomita *et al.* 2003; Kato *et al.* 2008; Schwenk *et al.* 2009, 2012; von Engelhardt *et al.* 2010; Shanks *et al.* 2012; Khodosevich *et al.* 2014). These proteins influence forward trafficking, subcellular localization and importantly gating kinetics of AMPA receptors (Priel *et al.* 2005; Tomita *et al.* 2005; Turetsky *et al.* 2005; Schwenk *et al.* 2009, 2012; von Engelhardt *et al.* 2010; Shanks *et al.* 2012; Khodosevich *et al.* 2014; Farrow *et al.* 2015). Proteomic studies suggested that each neuron type expresses a unique set of auxiliary subunits (Schwenk *et al.* 2014). This explains the variability of gating properties of AMPA receptors in different neuron types (Geiger *et al.* 1995) and also the fact that the properties of native AMPA receptors differ considerably from the properties of heterologously expressed tetrameric AMPA receptors. It is therefore likely that the presence of certain auxiliary subunits in native AMPA receptor complexes of dLGN neurons is the reason for the particularly slow recovery from desensitization. Most auxiliary subunits increase or do not affect the rate of recovery from desensitization (Jacobi & von Engelhardt, 2018, 2021). In fact, only three of the known auxiliary subunits decrease the rate of recovery from desensitization, namely CKAMP39, CKAMP44 and GSG1L (von Engelhardt *et al.* 2010; Schwenk *et al.* 2012; Shanks *et al.* 2012; Khodosevich *et al.* 2014; von Engelhardt, 2019). *In situ* hybridization data from our lab and the Allen Brain Atlas suggested that CKAMP39 is not expressed in the dLGN, in contrast to CKAMP44 and GSG1L (Lein *et al.* 2007; Farrow *et al.* 2015; Jacobi & von Engelhardt, 2017; Chen *et al.* 2018). Because the mRNA expression is comparably low for GSG1L and high for CKAMP44 in the dLGN (Lein *et al.* 2007), we hypothesized that an interaction with CKAMP44 explains the particularly slow recovery from desensitization of AMPA receptors in retinogeniculate synapses. Indeed, deletion of CKAMP44 accelerated the recovery from desensitization ($\tau_{recovery}$: wild type = 323 ms, CKAMP44$^{-/-}$ = 66 ms) (Chen *et al.* 2018). In addition, the amplitude of synaptic and extrasynaptic AMPA receptor-mediated currents was decreased to ∼50% (Chen *et al.* 2018), consistent with a role of CKAMP44 in promoting the trafficking of AMPA receptors to the cell surface and/or stabilization of AMPA receptors in the synapse by interaction with PDZ domain-containing proteins (Khodosevich *et al.* 2014). As expected from the increased rate of recovery from desensitization of AMPA receptors, paired-pulse ratios of EPSCs in retinogeniculate synapses were significantly increased in CKAMP44$^{-/-}$ mice (Chen *et al.* 2018). Thus, CKAMP44 is indeed the auxiliary subunit that is responsible for the slow recovery from desensitization of AMPA receptors and consequently for the short-term depression in retinogeniculate synapses (Fig. 2). Although CKAMP44 also increases the number of AMPA receptors and influences their gating in corticogeniculate synapses, short-term plasticity is not affected by CKAMP44 in this synapse type. This is unexpected as this this synapse has a very low resting release probability of 0.09 (Granseth & Lindstrom, 2003). Thus, the probability of two consecutive vesicle releases during repetitive activation of one synapse is low (Granseth & Lindstrom, 2003).

The prototypical AMPA receptor auxiliary subunit TARP γ-2 and TARP γ-4 are also expressed in dLGN relay neurons (Louros *et al.* 2014) (Fig. 2). TARP γ-2 controls retinogeniculate synapse function by augmenting the number of synaptic AMPA receptors (Louros *et al.* 2014). Interestingly, the rectification of EPSCs in retinogeniculate synapses is reduced in TARP γ-2$^{-/-}$ mice (Louros *et al.* 2014), indicating that TARP γ-2 increases preferentially the number of GluA2-lacking Ca^{2+}-permeable AMPA receptors in retinogeniculate synapses. In addition, the influence of TARP γ-2 on AMPA receptors contributes to homeostatic plasticity and is involved in the developmental refinement of retinogeniculate synapse function (Louros *et al.* 2014). The role of TARP γ-2 and TARP γ-4 in short-term plasticity of retinogeniculate synapses has not been investigated yet. TARP γ-2 increases the rate of recovery from desensitization of GluA1 homomeric receptors (Priel *et al.* 2005; Gill *et al.* 2012; Devi *et al.* 2020). The influence of TARP γ-2 on short-term plasticity may therefore be opposite to that of CKAMP44. Reduction of visual experience by late dark rearing of mice increases the expression of TARP γ-2 in the dLGN, which may explain changes in AMPA receptor function such as decreased rectification (Louros *et al.* 2014). It would be interesting to investigate whether this also leads to an increased rate of recovery from desensitization of AMPA receptors and consequently to reduced short-term depression. The influence of TARP γ-4 on recovery from desensitization depends on the AMPA receptor subunit. Thus, TARP γ-4 increases the rate of recovery from desensitization of GluA1 homomeric AMPA receptors (Devi *et al.* 2020), but has the opposite influence on GluA2 homomeric AMPA

receptors (Cais *et al*. 2014). TARP γ-4 could therefore in theory increase or decrease short-term depression in retinogeniculate synapses, depending on the AMPA receptor composition.

Similar to TARP γ-4, TARP γ-8 also increases the rate of recovery from desensitization of GluA1 homomeric AMPA receptors (Devi *et al*. 2020) but decreases the rate of recovery from desensitization of GluA2 homomeric AMPA receptors (Cais *et al*. 2014). TARP γ-8 in fact influences short-term plasticity in dentate gyrus granule cells (Khodosevich *et al*. 2014). Thus, paired-pulse ratios of EPSCs in medial and lateral path synapses are decreased in dentate gyrus granule cells of TARP γ-8$^{-/-}$ mice. CKAMP44 exerts the opposite influence on recovery from desensitization of AMPA receptors and short-term plasticity in these synapses (Khodosevich *et al*. 2014). However, it is not very likely that TARP γ-8 plays a strong role in short-term plasticity in retinogeniculate synapses considering the low level of *cacng8* mRNA expression (the gene *cacng8* codes for TARP γ-8) in the dLGN in the Allen Brain Atlas (Lein *et al*. 2007).

GSG1L mRNA is expressed in the dLGN at low levels (Lein *et al*. 2007). Similar to CKAMP44, GSG1L reduces the rate of recovery from desensitization (Schwenk *et al*. 2012; Shanks *et al*. 2012) and might therefore be partly responsible for the short-term depression in retinogeniculate synapses. There is currently no functional data on the role of GSG1L in the dLGN. Interestingly, GSG1L affects short-term plasticity by decreasing the rate of recovery from desensitization in another thalamic nucleus. While GSG1L expression level is low in most thalamic nuclei including the dLGN, there is a particularly high expression in anterior thalamus (Lein *et al*. 2007; Kamalova *et al*. 2020). GSG1L influences short-term plasticity specifically of excitatory inputs from the cortex but not from subiculum or the mammillary bodies to neurons of the anterior thalamus (Kamalova *et al*. 2020). The reason for the pathway specificities of the influences of GSG1L and CKAMP44 in anterior thalamus and dLGN, respectively, are, however, quite different. As discussed above, the differences in vesicle release probability explain the fact that CKAMP44 modulates short-term plasticity in retinogeniculate but not corticogeniculate synapses (Chen *et al*. 2018). In contrast, release probability is similar in corticothalamic and subiculum-thalamic synapses and even higher in mammillothalamic synapses in the anterior thalamus, at least when estimating release probability from paired-pulse ratios (Kamalova *et al*. 2020). Consistently, AMPA receptor desensitization affects short-term plasticity not only in corticothalamic but also mammillothalamic synapses in the anterior thalamus (Kamalova *et al*. 2020). One reason for a pathway-specific effect of GSG1L on short-term plasticity may be a preferential localization of GSG1L-containing AMPA receptors in corticothalamic synapses and low or no expression in mammillothalamic and subiculum-thalamic synapses. In addition, TARP γ-2 is contained in AMPA receptors of mammillothalamic and subiculum-thalamic synapses and the influence of TARP γ-2 on AMPA receptor gating seems to be dominant thereby masking effects of GSG1L (Kamalova *et al*. 2020).

The study of Kamalova and colleagues (2020) shows that it is thus far not possible to predict AMPA receptor function in a specific synapse even if the expression of all the AMPA receptor subunits and auxiliary subunits were known. One reason for this is the specific subcellular localization (e.g. in only one synapse type) of particular AMPA receptor complexes. Another reason is that the influence of auxiliary subunits depends on the AMPA receptor complex composition. For example, as discussed above, TARP γ-4 and TARP γ-8 increase the rate of recovery from desensitization of GluA1 homomeric AMPA receptors (Devi *et al*. 2020) but decrease the rate of GluA2 homomeric AMPA receptors (Cais *et al*. 2014). In addition, little is known about the influence of auxiliary subunits on native heteromeric AMPARs, which also contain other auxiliary subunits. For example, AMPA receptors in dentate gyrus granule cells contain CKAMP44 and TARP γ-8 and the presence of one subunit may modulate the influence of the other subunit (Khodosevich *et al*. 2014). Another example is the influence of CNIH-2 on gating properties, which depends not only on the AMPA receptor subunit but also on the presence of TARPs. CNIH-2 reduces the rate of recovery from desensitization of GluA1 homomers but increases the rate of recovery from desensitization of TARP γ-2-containing GluA1 homomers (Gill *et al*. 2012). The dependence of the influence of a given auxiliary subunit on the AMPA receptor composition and presence of other auxiliary subunits may also explain why AMPA receptor desensitization is very fast in dLGN relay neurons (desensitization rate = 2.07 ms) (Chen *et al*. 2018) despite the presence of TARP γ-2 and TARP γ-4, which slow desensitization of all homomeric and of GluA1/2 heteromeric AMPA receptors (Tomita *et al*. 2005; Korber, 2007; Soto *et al*. 2009; Cais *et al*. 2014).

Anatomy of retinogeniculate synapse

In the previous paragraphs, I discussed evidence that high vesicle release probability and the particular kinetics of CKAMP44-interacting AMPA receptors are prerequisites for the influence of desensitization on short-term depression in retinogeniculate synapses. However, data from freeze fracture replica immunolabelling, electrophysiology and simulations showed the specific anatomical properties of retinogeniculate synapses are also relevant for the strong synaptic short-term depression

(Budisantoso *et al.* 2012). Retinal ganglion cell axons contact relay neurons of the dLGN with several large terminals comprising many active zones (Famiglietti & Peters, 1972; Rafols & Valverde, 1973; Budisantoso *et al.* 2012). From electrophysiological analyses in acute brain slices of juvenile mice, Chinfei Chen and Wade Regehr found that activation of a dominant retinal ganglion cell input onto a dLGN relay neuron results in an EPSC with an average amplitude of 1220 pA. Considering the amplitude of mEPSCs and release probability, they estimated that such a dominant connection comprises 125–250 release site (Chen & Regehr, 2000). Each terminal contains on average 6 (complex type) or 27 (simple type) release sites, with a distance of 700 nm between release sites (Budisantoso *et al.* 2012). The geometry of mouse retinogeniculate synapses (Rafols & Valverde, 1973; Bickford *et al.* 2010) precludes fast diffusion of glutamate out of the synaptic cleft and allows spillover of glutamate from active to non-active neighbouring release sites (Fig. 3). Budisantoso *et al.* simulated the spillover of glutamate from an active to a non-active neighbouring release site. They showed that the peak

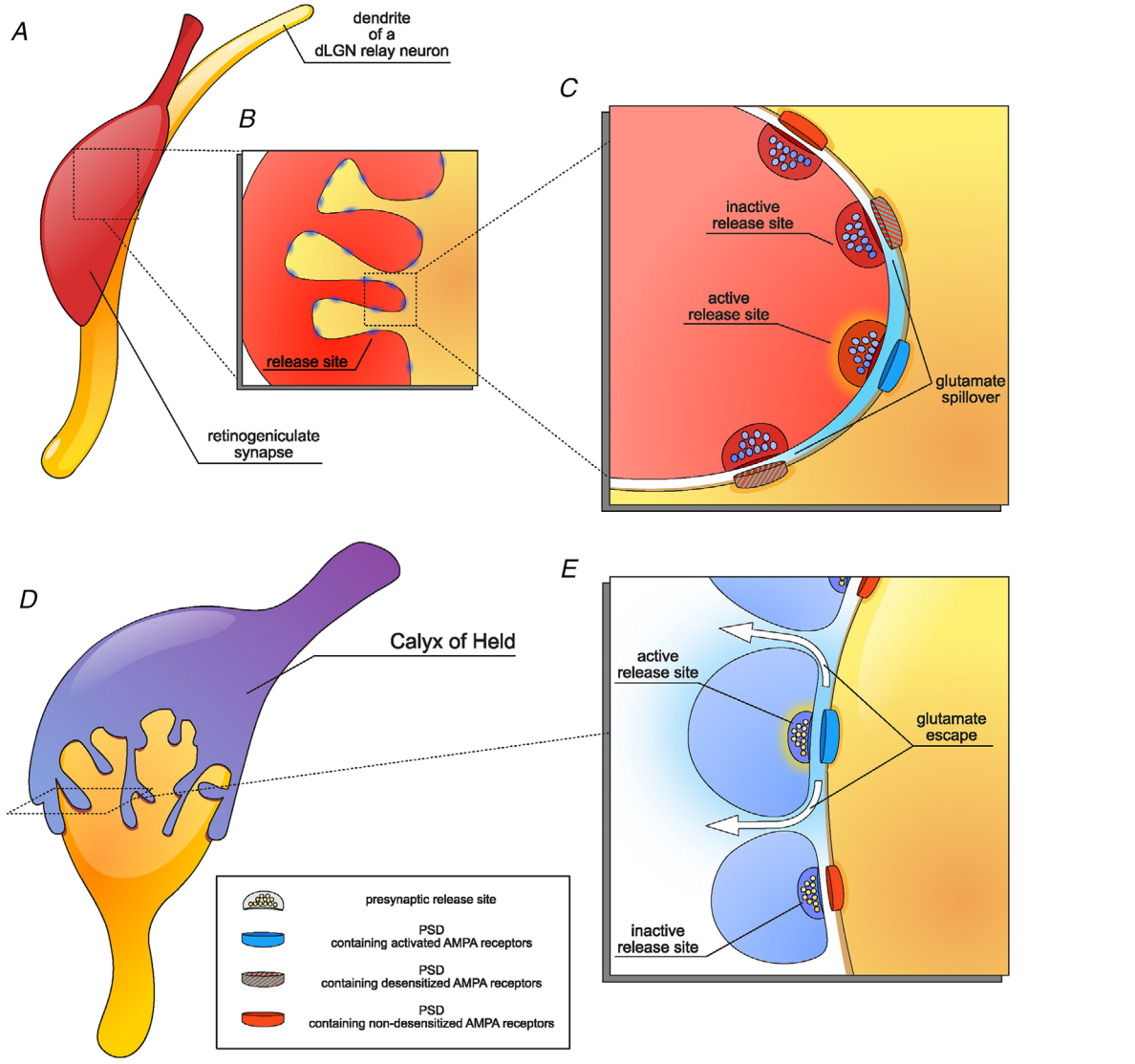

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Figure 3. Transmission in retinogeniculate synapses and the calyx of Held
A and *B*, the non-fenestrated large retinogeniculate synapse (enlarged in *C*) promotes spillover of glutamate from active to non-active release site. AMPA receptors at non-active release sites are desensitized by spillover glutamate. *D*, the highly fenestrated calyx of Held of the adult rodent allows glutamate to quickly escape the synaptic cleft such that AMPA receptors at non-active synapses (*E*) do not desensitize from spillover of glutamate from neighbouring active synapse.

glutamate concentration (∼100 μM) at non-active release site is not high enough to open a substantial number of AMPA receptors but sufficiently high to desensitize more than half of the AMPA receptors (Budisantoso *et al*. 2012). In fact, based on their simulation, glutamate escapes so slowly out of the synaptic cleft that ∼30% of AMPA receptors at this non-active neighbouring release site are desensitized 100 ms after the vesicle release (Budisantoso *et al*. 2012). This suggested that glutamate spillover contributes significantly to the short-term depression at retinogeniculate synapse. Indeed, simulations showed that the paired-pulse ratio of AMPA receptor-mediated EPSCs (interstimulus interval = 50 ms) doubles without spillover of glutamate (Budisantoso *et al*. 2012).

However, it is not only the large synapse size with its many release sites that explains the role of spillover glutamate in short-term plasticity in certain synapses, but also how readily glutamate escapes the synaptic cleft. The role of the ultrastructure of the synapse for short-term plasticity has been demonstrated in detail at the calyx of Held, which is also a large synapse that contains many release sites (678 in the adult and calyx of Held) (Taschenberger *et al*. 2002). AMPA receptor desensitization shapes short-term plasticity in the developing calyx of Held and calyx-type synapses (Trussell *et al*. 1993; Isaacson & Walmsley, 1996; Otis *et al*. 1996; Taschenberger *et al*. 2002; Renden *et al*. 2005). At postnatal day 8-10, the synaptic cleft of the calyx is – similar to retinogeniculate synapses (Budisantoso *et al*. 2012; Morgan *et al*. 2016) – a contiguous sheath that prevents glutamate diffusion out of the synaptic cleft (Satzler *et al*. 2002; Taschenberger *et al*. 2002). In addition, multivesicular release increases the pooled glutamate concentration in the developing calyx of Held (Taschenberger *et al*. 2002). The prolonged presence of glutamate in the developing calyx of Held desensitizes AMPA receptors and thus shapes short-term plasticity (Taschenberger *et al*. 2002).

In the adult calyx of Held, AMPA receptor desensitization plays little role in short-term plasticity (Koike-Tani *et al*. 2008). This can be explained by a developmental reduction in release probability and likelihood of multivesicular release (Meyer *et al*. 2001; Taschenberger *et al*. 2002; Koike-Tani *et al*. 2008). In addition, the recovery from desensitization of AMPA receptors accelerates with development of the calyx of Held (Joshi *et al*. 2004; Koike-Tani *et al*. 2008). In fact, the recovery from desensitization is an order of magnitude faster than the recovery of AMPA receptors in dLGN neurons (Chen *et al*. 2018). However, an important additional reason for little contribution of AMPAR desensitization to short-term plasticity in the adult calyx of Held is that synapse ultrastructure changes with development. Thus, the adult calyx of Held is highly fenestrated which allows glutamate to quickly exit the synaptic cleft (Kandler & Friauf, 1993; Iwasaki & Takahashi, 2001; Taschenberger *et al*. 2002; Ford *et al*. 2009) (Fig. 3). Hence, a combination of low release probability, fast escape of glutamate out of the synaptic cleft and fast recovery from desensitization of AMPA receptors explains the absence of a role of desensitization for short-term plasticity, which is important for ensuring transfer of auditory information in the kilohertz range with high fidelity.

Long dwell time of glutamate in the synaptic cleft is not unique for retinogeniculate synapses, but explains the role of AMPA receptor desensitization in short-term plasticity also in other central synapses, such as mossy fibre-unipolar brush cell synapses. Glutamate escapes these morphologically tortuous giant synapses only slowly (Rossi *et al*. 1995; Kinney *et al*. 1997). In fact, glutamate is entrapped for periods of several seconds (5–6 s) in this synapse (Kinney *et al*. 1997). This explains the biphasic EPSPC waveform with a fast component, which results from the fast activation of AMPA receptors with high glutamate concentration, and a slow component, which results from AMPA receptors that open as they recover from desensitization when glutamate concentration falls. Interestingly, the current amplitude increases after a few hundred milliseconds of the slow component of the EPSC. This has been explained with a bell-shaped dose-response relationship of steady-state AMPA receptor-mediated currents leading to increased opening of AMPA receptors when the decaying glutamate in the synaptic cleft reaches a concentration of ∼10 μM (Kinney *et al*. 1997). Interestingly, a bell-shaped shaped dose-response relationship has been described for TARP γ-2-containing AMPA receptors (Morimoto-Tomita *et al*. 2009). TARP γ-2 indeed plays a role in mossy fibre-unipolar brush cell synapses. Genetic deletion of TARP γ-2 renders the dose-response relationship monotonic and consequently reduces the amplitude of the slow EPCS component (Lu *et al*. 2017).

Glutamate spillover from one release site to neighbouring release sites is a prerequisite for a role of AMPA receptor desensitization in short-term plasticity in low-release probability synapses that rarely have two consecutive vesicles released when stimulated twice in short time periods. Thus, AMPA receptor desensitization does not affect short-term in cortico-geniculate synapses (Granseth, 2004), even though they also express CKAMP44-containing AMPA receptors (Chen *et al*. 2018), because they are small and show a low release probability (P_r ∼0.1) (Granseth & Lindstrom, 2003). As shown in synapses of the hippocampus (Hestrin *et al*. 1990; Isaacson & Nicoll, 1993; Sarantis *et al*. 1993), glutamate can rapidly escape small bouton-like terminals, thereby reducing AMPA receptor desensitization. In addition, corticogeniculate synapses have few or only one release site (Granseth & Lindstrom, 2003), which reduces

the likelihood that spillover glutamate desensitizes AMPA receptors at neighbouring release sites.

Spillover of glutamate can occur not only from one release site to another in, for example, retinogeniculate synapses but also from one synapse to a neighbouring synapse. For example, there is evidence for spillover of glutamate from active to non-active synapses in the hippocampus (Kullmann *et al.* 1996). Estimates suggest that peak glutamate concentration can be 50–100 μM in non-active synapses at a distance of 500 nm from the releasing synapse, sufficiently high to activate NMDA but not AMPA receptors in a neighbouring synapse (Rusakov & Kullmann, 1998; Rusakov *et al.* 1999). The extent of this intersynaptic cross-talk in the hippocampus, however, is limited by the fast removal of glutamate by glutamate transporter (Asztely *et al.* 1997). Glutamate transporters also reduce glutamate accumulation in mossy fibre-unipolar brush cell synapses and thereby shorten EPSC duration and AMPA receptor desensitization (Lu *et al.* 2017; Balmer *et al.* 2021). In contrast, glutamate transporters do not significantly contribute to removal of glutamate from the synaptic cleft of the developing and adult calyx of Held, although they are relevant for the reduction of the ambient extrasynaptic glutamate concentration (Renden *et al.* 2005). This suggests that slow diffusion of glutamate out of the synaptic cleft and not insufficient glutamate removal explains the desensitization of AMPA receptors in the immature calyx of Held.

In the dLGN, the glutamate transporters GLT-1 and GLAST are expressed. Pharmacological block of glutamate transporters (GLT-1 in particular) slows the decay of AMPA receptor and NMDA receptor-mediated currents and marginally decreases the paired-pulse ratio (Budisantoso *et al.* 2012; Hauser *et al.* 2013). This suggests that glutamate transporters effectively reduce glutamate concentrations within a retinogeniculate synapse. In addition, they may reduce extrasynaptic glutamate concentration and thereby prevent spillover of glutamate from one synapse to a neighbouring synapse in the dLGN.

Role of short-term depression in processing of visual information

Is short-term depression relevant for processing of visual information? It is well known that the dLGN is not a simple relay station that receives information from the retina, which is then send to the visual cortex. *In vivo* analysis of axonal and neuronal activity showed that dLGN neurons fire fewer spikes than retinal ganglion cell axons (Lee *et al.* 1983; Kaplan *et al.* 1987; Usrey *et al.* 1998; Carandini *et al.* 2007; Sincich *et al.* 2007; Weyand, 2007). Ganglion cells of the mouse retina fire with peak firing rates of up to 500 Hz in response to optimal stimuli (Zeck & Masland, 2007; Cui *et al.* 2016; Jacoby & Schwartz, 2017; Krieger *et al.* 2017). Thus, it is very likely that short-term depression and AMPA receptor desensitization in retinogeniculate synapses affect transmission of visual information. Indeed, we found that accelerating the recovery from desensitization of AMPA receptors by genetic deletion of CKAMP44 increased not only the paired-pulse ratio of EPSCs in retinogeniculate synapses but also dLGN spike probability in acute brain slices, as well as peak firing rates of On and Off responses of dLGN neurons to full-field On and Off stimuli *in vivo* (Chen *et al.* 2018) (Fig. 4).

It is a known concept that short-term plasticity affects filter properties of synapses. For example, the facilitating corticogeniculate synapses act as high pass filters (Granseth, 2004). Thus, depolarization and firing probability will increase with action potential frequency and number of cortical inputs. It has been hypothesized that this positive feedback system functions thereby as an amplifier of relevant visual stimuli (Granseth, 2004). In contrast to that, the pronounced short-term depression of EPSCs should shift the filter properties of retinogeniculate synapses in the direction of a low pass filter. This is at first glance not compatible with the observation that transmission of visual information is most effective when retinal ganglion cells fire at high frequency. Spike transmission rate is significantly higher for the second action potential than for the first, if inter-event intervals are shorter than 30 ms (Mastronarde, 1987; Carandini *et al.* 2007; Sincich *et al.* 2007; Weyand, 2007; Alitto *et al.* 2011). The increase in transmission rate at high firing frequency can be explained by the fact that absolute EPSP amplitudes indeed summate and therefore increase during high frequency stimulation, although the single EPSC and relative EPSP amplitudes decrease (Blitz & Regehr, 2003; Carandini *et al.* 2007; Chen *et al.* 2018) (Fig. 4*B*). Of note, currents that are mediated by NMDA receptors in retinogeniculate synapses contribute substantially to the depolarization of relay neurons. Due to the Mg^{2+}-block of the receptors at lower membrane potentials, the contribution of NMDA receptor-mediated currents increases with activity rates of retinogeniculate synapses and depolarization of the dLGN relay cells (Blitz & Regehr, 2003; Augustinaite & Heggelund, 2007). NMDA receptor-mediated currents play a role in activating dLGN neurons particularly during development when AMPA receptor number per retinogeniculate synapse is still comparably low. The expression of GluN2B-, GluN2C-, and GluN2D-containing NMDA receptors, which deactivate slowly and show only a moderate Mg^{2+} block, facilitates the long-lasting opening of NMDA receptors and thereby strengthens the contribution to transmission in retinogeniculate synapses during development (Liu & Chen, 2008).

The contribution of short-term depression to transmission rates decreases when retinal ganglion cells fire with high frequency for a prolonged time-period. Thus, Carandini and colleagues found little evidence for changes in EPSC amplitudes in retinogeniculate synapses of awake macaques during continuous noise stimulus presentation (Carandini *et al*. 2007). The activity of the analysed retinal ganglion cell axons was very high (most of the time of the stimulus presentation in the range of 50–100 Hz), which explains the absence of short-term depression of EPSCs. Short-term depression decreases synaptic strength most effectively after a period of silence or low firing frequency. Steady-state depression of EPSC amplitudes is reached after ∼10 action potentials of retinal ganglion cells (Chen *et al*. 2018) (Fig. 4*A*). During continuous high firing frequency, EPSC amplitudes change very little and a considerable proportion of AMPA receptors are continuously desensitized (Chen *et al*. 2018). This affects synaptic strength as evidenced by increased steady-state EPSC amplitudes in retinogeniculate synapses with AMPA receptors that recover quickly from desensitization (i.e. in CKAMP44$^{-/-}$ mice) (Chen *et al*. 2018). In fact the deletion of CKAMP44 increased steady-state EPSC amplitudes even when stimulating retinogeniculate synapses at low frequencies of 1 Hz (Chen *et al*. 2018). Thus, AMPA receptor desensitization

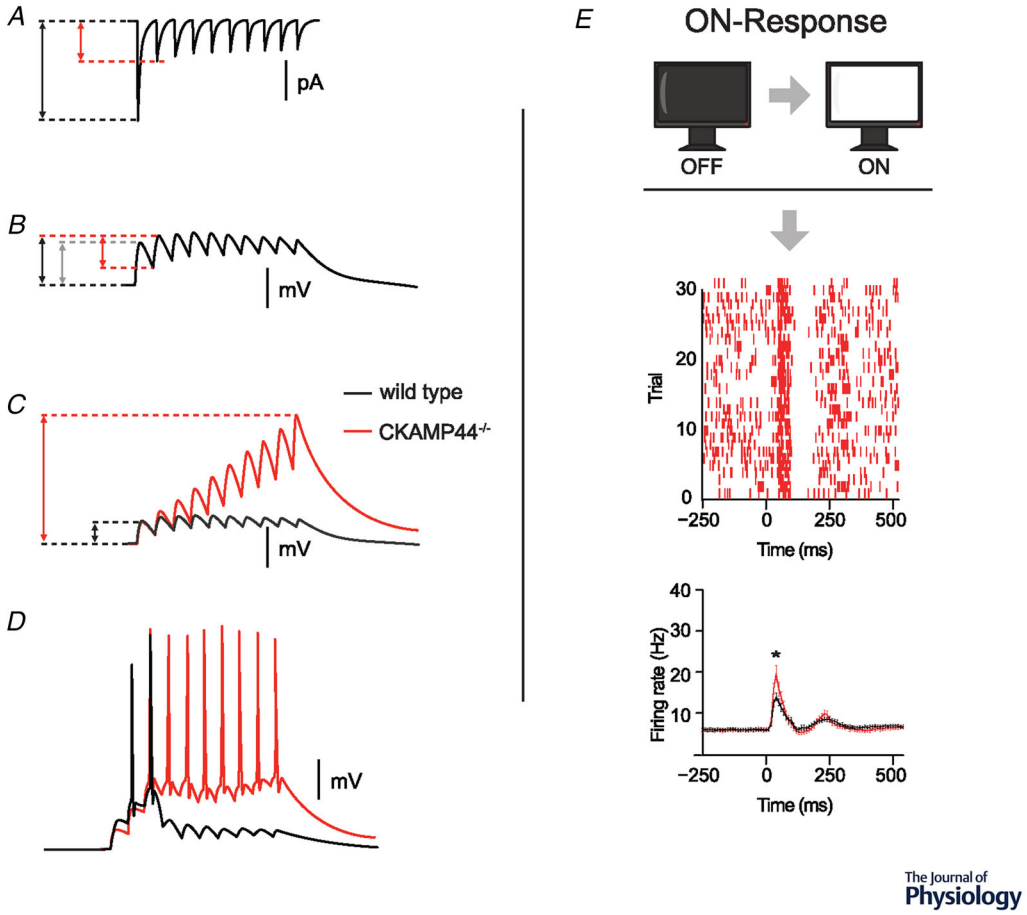

Figure 4. Effect of CKAMP44 deletion on retinogeniulate synapse function and dLGN neuron firing rates
A, short-term depression of EPSCs in retinogeniculate synapses that were stimulated with 50 Hz. *B*, EPSP in retinogeniculate synapses in response to a 50 Hz stimulus. Absolute EPSP amplitudes increase despite a reduction in the relative EPSP amplitude due to summation. *C*, EPSP amplitudes increase in retinogeniulate synapses of CKAMP44$^{-/-}$ mice considerably more than in wild-type mice, which is explained by the faster recovery from desensitization of AMPA receptors that do not interact with CKAMP44. *D*, strong stimulation of retinogeniculate synapses with 50 Hz evokes significantly more action potentials in relay neurons of CKAMP44$^{-/-}$ than in wild-type mice. *E*, peak firing rate of on responses of dLGN neurons are increased in CKAMP44$^{-/-}$ mice. Tetrode recordings of dLGN neurons were performed in non-anaesthetized mice. Raster plot shows spikes (in red) of a dLGN neuron that increases firing rate shortly after briefly increasing the light intensity of the monitor. The quantification shows the increase in peak firing rate in dLGN neurons of CKAMP44$^{-/-}$ mice (bottom; $N = 542$ dLGN neurons in 6 wild-type and 430 dLGN neurons in 6 CKAMP44$^{-/-}$ mice; mean ± SEM). CKAMP44 deletion also increased Off responses. (Adapted from Chen *et al*. 2018.)

should also decrease transfer rates when a mouse is looking at a grey monitor of average luminance, when retinal ganglion cells fire with 'background' firing rates of approximately 1–10 Hz (Sagdullaev & McCall, 2005).

Steady-state AMPA receptor desensitization would therefore contribute to mechanisms that enhance signal-to-noise ratios of dLGN neuron activity. As mentioned, spike transmission rate is significantly higher for a second action potential than for a first if inter-event intervals are shorter than 30 ms (Mastronarde, 1987; Carandini *et al*. 2007; Sincich *et al*. 2007; Weyand, 2007; Alitto *et al*. 2011). Steady-state depression of AMPA receptors would lower the transmission rate of the first spike especially during high overall activity of retinal ganglion cells. Summation of EPSPs increases the spike transmission rate during the second action potential (Carandini *et al*. 2007; Chen *et al*. 2018). This is highly relevant for the role of the dLGN in processing visual information, as *in vivo* recordings from retinal ganglion cells and connected dLGN neurons showed that the second action potential carries more visual information than the first action potential (Usrey *et al*. 1998; Rathbun *et al*. 2010). The strength of retinogeniculate synapses must therefore be fine-tuned such that dLGN neurons do not fire to spikes that carry little information (noise) but that they fire during presentation of weak visual stimuli when only few (maybe only one) retinal ganglion cells fire two action potentials. Retinogeniculate synapses must be strong enough that the depolarization in response to two action potentials is sufficient to reach threshold potential. This bears the risk that dLGN neurons quickly saturate during high retinal ganglion cell activity. AMPA receptor desensitization and short-term depression of retinogeniculate synapses would prevent this saturation and thereby increases the dynamic range of dLGN relay neurons.

References

Alitto HJ, Moore BDt, Rathbun DL & Usrey WM (2011). A comparison of visual responses in the lateral geniculate nucleus of alert and anaesthetized macaque monkeys. *J Physiol* **589**, 87–99.

Asztely F, Erdemli G & Kullmann DM (1997). Extrasynaptic glutamate spillover in the hippocampus: dependence on temperature and the role of active glutamate uptake. *Neuron* **18**, 281–293.

Augustinaite S & Heggelund P (2007). Changes in firing pattern of lateral geniculate neurons caused by membrane potential dependent modulation of retinal input through NMDA receptors. *J Physiol* **582**, 297–315.

Balmer TS, Borges-Merjane C & Trussell LO (2021). Incomplete removal of extracellular glutamate controls synaptic transmission and integration at a cerebellar synapse. *Elife* **10**, e63819.

Bickford ME (2019). Synaptic organization of the dorsal lateral geniculate nucleus. *Eur J Neurosci* **49**, 938–947.

Bickford ME, Slusarczyk A, Dilger EK, Krahe TE, Kucuk C & Guido W (2010). Synaptic development of the mouse dorsal lateral geniculate nucleus. *J Comp Neurol* **518**, 622–635.

Blitz DM & Regehr WG (2003). Retinogeniculate synaptic properties controlling spike number and timing in relay neurons. *J Neurophysiol* **90**, 2438–2450.

Budisantoso T, Matsui K, Kamasawa N, Fukazawa Y & Shigemoto R (2012). Mechanisms underlying signal filtering at a multisynapse contact. *J Neurosci* **32**, 2357–2376.

Burnashev N, Monyer H, Seeburg PH & Sakmann B (1992). Divalent ion permeability of AMPA receptor channels is dominated by the edited form of a single subunit. *Neuron* **8**, 189–198.

Cais O, Herguedas B, Krol K, Cull-Candy SG, Farrant M & Greger IH (2014). Mapping the interaction sites between AMPA receptors and TARPs reveals a role for the receptor N-terminal domain in channel gating. *Cell Rep* **9**, 728–740.

Carandini M, Horton JC & Sincich LC (2007). Thalamic filtering of retinal spike trains by postsynaptic summation. *J Vis* **7**, 21–11.

Chanda S & Xu-Friedman MA (2010). A low-affinity antagonist reveals saturation and desensitization in mature synapses in the auditory brain stem. *J Neurophysiol* **103**, 1915–1926.

Chen C, Blitz DM & Regehr WG (2002). Contributions of receptor desensitization and saturation to plasticity at the retinogeniculate synapse. *Neuron* **33**, 779–788.

Chen C & Regehr WG (2000). Developmental remodeling of the retinogeniculate synapse. *Neuron* **28**, 955–966.

Chen L, Bao S, Qiao X & Thompson RF (1999). Impaired cerebellar synapse maturation in waggler, a mutant mouse with a disrupted neuronal calcium channel gamma subunit. *Proc Natl Acad Sci U S A* **96**, 12132–12137.

Chen L, Chetkovich DM, Petralia RS, Sweeney NT, Kawasaki Y, Wenthold RJ, Bredt DS & Nicoll RA (2000). Stargazin regulates synaptic targeting of AMPA receptors by two distinct mechanisms. *Nature* **408**, 936–943.

Chen L, El-Husseini A, Tomita S, Bredt DS & Nicoll RA (2003). Stargazin differentially controls the trafficking of alpha-amino-3-hydroxyl-5-methyl-4-isoxazolepropionate and kainate receptors. *Mol Pharmacol* **64**, 703–706.

Chen XF, Aslam M, Gollisch T, Allen K & von Engelhardt J (2018). CKAMP44 modulates integration of visual inputs in the lateral geniculate nucleus. *Nat Commun* **9**, 261.

Chen XF, Wang DN, Kegel M & von Engelhardt J (2019). Electrophysiological investigations of retinogeniculate and corticogeniculate synapse function. *Jove-J Vis Exp* (**150**), e59680.

Cox CL & Beatty JA (2017). The multifaceted role of inhibitory interneurons in the dorsal lateral geniculate nucleus. *Vis Neurosci* **34**, E017.

Cui Y, Wang YV, Park SJ, Demb JB & Butts DA (2016). Divisive suppression explains high-precision firing and contrast adaptation in retinal ganglion cells. *Elife* **5**, e19460.

Devi SPS, Cheng Y, Tomita S, Howe JR & Zhang W (2020). TARPs modulate receptor-mediated paired-pulse depression and recovery from desensitization. *J Neurosci* **40**, 8233–8247.

Famiglietti EV, Jr. & Peters A (1972). The synaptic glomerulus and the intrinsic neuron in the dorsal lateral geniculate nucleus of the cat. *J Comp Neurol* **144**, 285-333.

Farrow P, Khodosevich K, Sapir Y, Schulmann A, Aslam M, Stern-Bach Y, Monyer H & von Engelhardt J (2015). Auxiliary subunits of the CKAMP family differentially modulate AMPA receptor properties. *Elife* **4**, e09693.

Fioravante D & Regehr WG (2011). Short-term forms of presynaptic plasticity. *Curr Opin Neurobiol* **21**, 269–274.

Ford MC, Grothe B & Klug A (2009). Fenestration of the calyx of Held occurs sequentially along the tonotopic axis, is influenced by afferent activity, and facilitates glutamate clearance. *J Comp Neurol* **514**, 92–106.

Geiger JR, Melcher T, Koh DS, Sakmann B, Seeburg PH, Jonas P & Monyer H (1995). Relative abundance of subunit mRNAs determines gating and Ca2+ permeability of AMPA receptors in principal neurons and interneurons in rat CNS. *Neuron* **15**, 193–204.

Gill MB, Kato AS, Wang H & Bredt DS (2012). AMPA receptor modulation by cornichon-2 dictated by transmembrane AMPA receptor regulatory protein isoform. *Eur J Neurosci* **35**, 182–194.

Granseth B (2004). Dynamic properties of corticogeniculate excitatory transmission in the rat dorsal lateral geniculate nucleus in vitro. *J Physiol* **556**, 135–146.

Granseth B, Ahlstrand E & Lindstrom S (2002). Paired pulse facilitation of corticogeniculate EPSCs in the dorsal lateral geniculate nucleus of the rat investigated in vitro. *J Physiol* **544**, 477–486.

Granseth B & Lindstrom S (2003). Unitary EPSCs of corticogeniculate fibers in the rat dorsal lateral geniculate nucleus in vitro. *J Neurophysiol* **89**, 2952–2960.

Grosskreutz J, Zoerner A, Schlesinger F, Krampfl K, Dengler R & Bufler J (2003). Kinetic properties of human AMPA-type glutamate receptors expressed in HEK293 cells. *Eur J Neurosci* **17**, 1173–1178.

Guido W (2018). Development, form, and function of the mouse visual thalamus. *J Neurophysiol* **120**, 211–225.

Gutig R, Gollisch T, Sompolinsky H & Meister M (2013). Computing complex visual features with retinal spike times. *PLoS One* **8**, e53063.

Hashimoto K, Fukaya M, Qiao X, Sakimura K, Watanabe M & Kano M (1999). Impairment of AMPA receptor function in cerebellar granule cells of ataxic mutant mouse stargazer. *J Neurosci* **19**, 6027–6036.

Hauser JL, Edson EB, Hooks BM & Chen C (2013). Metabotropic glutamate receptors and glutamate transporters shape transmission at the developing retinogeniculate synapse. *J Neurophysiol* **109**, 113–123.

Hauser JL, Liu X, Litvina EY & Chen C (2014). Prolonged synaptic currents increase relay neuron firing at the developing retinogeniculate synapse. *J Neurophysiol* **112**, 1714–1728.

Hestrin S, Sah P & Nicoll RA (1990). Mechanisms generating the time course of dual component excitatory synaptic currents recorded in hippocampal slices. *Neuron* **5**, 247–253.

Hollmann M, Hartley M & Heinemann S (1991). Ca^{2+} permeability of KA-AMPA-gated glutamate receptor channels depends on subunit composition. *Science* **252**, 851–853.

Isaacson JS & Nicoll RA (1993). The uptake inhibitor L-trans-PDC enhances responses to glutamate but fails to alter the kinetics of excitatory synaptic currents in the hippocampus. *J Neurophysiol* **70**, 2187–2191.

Isaacson JS & Walmsley B (1996). Amplitude and time course of spontaneous and evoked excitatory postsynaptic currents in bushy cells of the anteroventral cochlear nucleus. *J Neurophysiol* **76**, 1566–1571.

Iwasaki S & Takahashi T (2001). Developmental regulation of transmitter release at the calyx of Held in rat auditory brainstem. *J Physiol* **534**, 861–871.

Jacobi E & von Engelhardt J (2017). Diversity in AMPA receptor complexes in the brain. *Curr Opin Neurobiol* **45**, 32–38.

Jacobi E & von Engelhardt J (2018). AMPA receptor complex constituents: Control of receptor assembly, membrane trafficking and subcellular localization. *Mol Cell Neurosci* **91**, 67–75.

Jacobi E & von Engelhardt J (2021). Modulation of information processing by AMPA receptor auxiliary subunits. *J Physiol* **599**, 471–483.

Jacoby J & Schwartz GW (2017). Three small-receptive-field ganglion cells in the mouse retina are distinctly tuned to size, speed, and object motion. *J Neurosci* **37**, 610–625.

Joshi I, Shokralla S, Titis P & Wang LY (2004). The role of AMPA receptor gating in the development of high-fidelity neurotransmission at the calyx of Held synapse. *J Neurosci* **24**, 183–196.

Kamalova A, Futai K, Delpire E & Nakagawa T (2020). AMPA receptor auxiliary subunit GSG1L suppresses short-term facilitation in corticothalamic synapses and determines seizure susceptibility. *Cell Rep* **32**, 107921.

Kandler K & Friauf E (1993). Pre- and postnatal development of efferent connections of the cochlear nucleus in the rat. *J Comp Neurol* **328**, 161–184.

Kaplan E, Purpura K & Shapley RM (1987). Contrast affects the transmission of visual information through the mammalian lateral geniculate nucleus. *J Physiol* **391**, 267–288.

Kato AS, Siuda ER, Nisenbaum ES & Bredt DS (2008). AMPA receptor subunit-specific regulation by a distinct family of type II TARPs. *Neuron* **59**, 986–996.

Kessler M, Suzuki E, Montgomery K & Arai AC (2008). Physiological significance of high- and low-affinity agonist binding to neuronal and recombinant AMPA receptors. *Neurochem Int* **52**, 1383–1393.

Khodosevich K, Jacobi E, Farrow P, Schulmann A, Rusu A, Zhang L, Sprengel R, Monyer H & von Engelhardt J (2014). Co-expressed auxiliary subunits exhibit distinct modulatory profiles on AMPA receptor function. *Neuron* **83**, 601–615.

Kielland A, Bochorishvili G, Corson J, Zhang L, Rosin DL, Heggelund P & Zhu JJ (2009). Activity patterns govern synapse-specific AMPA receptor trafficking between deliverable and synaptic pools. *Neuron* **62**, 84–101.

Kielland A & Heggelund P (2002). AMPA and NMDA currents show different short-term depression in the dorsal lateral geniculate nucleus of the rat. *J Physiol* **542**, 99–106.

Kinney GA, Overstreet LS & Slater NT (1997). Prolonged physiological entrapment of glutamate in the synaptic cleft of cerebellar unipolar brush cells. *J Neurophysiol* **78**, 1320–1333.

Koike-Tani M, Kanda T, Saitoh N, Yamashita T & Takahashi T (2008). Involvement of AMPA receptor desensitization in short-term synaptic depression at the calyx of Held in developing rats. *J Physiol* **586**, 2263–2275.

Korber C, Werner M, Kott S, Ma Z-L, & Hollmann M (2007) The transmembrane AMPA receptor regulatory protein gamma 4 is a more effective modulator of AMPA receptor function than stargazin (gamma 2). *J Neurosci* **27**, 8442–8447.

Krieger B, Qiao M, Rousso DL, Sanes JR & Meister M (2017). Four alpha ganglion cell types in mouse retina: Function, structure, and molecular signatures. *PLoS One* **12**, e0180091.

Kullmann DM, Erdemli G & Asztely F (1996). LTP of AMPA and NMDA receptor-mediated signals: evidence for presynaptic expression and extrasynaptic glutamate spill-over. *Neuron* **17**, 461–474.

Lee BB, Virsu V & Creutzfeldt OD (1983). Linear signal transmission from prepotentials to cells in the macaque lateral geniculate nucleus. *Exp Brain Res* **52**, 50–56.

Lein ES, Hawrylycz MJ, Ao N, Ayres M, Bensinger A, Bernard A, Boe AF, Boguski MS, Brockway KS, Byrnes EJ, Chen L, Chen L, Chen TM, Chin MC, Chong J, Crook BE, Czaplinska A, Dang CN, Datta S, Dee NR, Desaki AL, Desta T, Diep E, Dolbeare TA, Donelan MJ, Dong HW, Dougherty JG, Duncan BJ, Ebbert AJ, Eichele G, Estin LK, Faber C, Facer BA, Fields R, Fischer SR, Fliss TP, Frensley C, Gates SN, Glattfelder KJ, Halverson KR, Hart MR, Hohmann JG, Howell MP, Jeung DP, Johnson RA, Karr PT, Kawal R, Kidney JM, Knapik RH, Kuan CL, Lake JH, Laramee AR, Larsen KD, Lau C, Lemon TA, Liang AJ, Liu Y, Luong LT, Michaels J, Morgan JJ, Morgan RJ, Mortrud MT, Mosqueda NF, Ng LL, Ng R, Orta GJ, Overly CC, Pak TH, Parry SE, Pathak SD, Pearson OC, Puchalski RB, Riley ZL, Rockett HR, Rowland SA, Royall JJ, Ruiz MJ, Sarno NR, Schaffnit K, Shapovalova NV, Sivisay T, Slaughterbeck CR, Smith SC, Smith KA, Smith BI, Sodt AJ, Stewart NN, Stumpf KR, Sunkin SM, Sutram M, Tam A, Teemer CD, Thaller C, Thompson CL, Varnam LR, Visel A, Whitlock RM, Wohnoutka PE, Wolkey CK, Wong VY, Wood M, Yaylaoglu MB, Young RC, Youngstrom BL, Yuan XF, Zhang B, Zwingman TA & Jones AR (2007). Genome-wide atlas of gene expression in the adult mouse brain. *Nature* **445**, 168–176.

Liang L & Chen C (2020). Organization, Function, and Development of the Mouse Retinogeniculate Synapse. *Annu Rev Vis Sci* **6**, 261–285.

Litvina EY & Chen C (2017). An evolving view of retinogeniculate transmission. *Vis Neurosci* **34**, E013.

Liu X & Chen C (2008). Different roles for AMPA and NMDA receptors in transmission at the immature retinogeniculate synapse. *J Neurophysiol* **99**, 629–643.

Lomeli H, Mosbacher J, Melcher T, Hoger T, Geiger JR, Kuner T, Monyer H, Higuchi M, Bach A & Seeburg PH (1994). Control of kinetic properties of AMPA receptor channels by nuclear RNA editing. *Science* **266**, 1709–1713.

Louros SR, Hooks BM, Litvina L, Carvalho AL & Chen C (2014). A role for stargazin in experience-dependent plasticity. *Cell Rep* **7**, 1614–1625.

Lu HW, Balmer TS, Romero GE & Trussell LO (2017). Slow AMPAR synaptic transmission is determined by stargazin and glutamate transporters. *Neuron* **96**, 73–80.e4.e74.

Lu W, Shi Y, Jackson AC, Bjorgan K, During MJ, Sprengel R, Seeburg PH & Nicoll RA (2009). Subunit composition of synaptic AMPA receptors revealed by a single-cell genetic approach. *Neuron* **62**, 254–268.

Mastronarde DN (1987). Two classes of single-input X-cells in cat lateral geniculate nucleus. II. Retinal inputs and the generation of receptive-field properties. *J Neurophysiol* **57**, 381–413.

Meyer AC, Neher E & Schneggenburger R (2001). Estimation of quantal size and number of functional active zones at the calyx of Held synapse by nonstationary EPSC variance analysis. *J Neurosci* **21**, 7889–7900.

Monavarfeshani A, Sabbagh U & Fox MA (2017). Not a one-trick pony: Diverse connectivity and functions of the rodent lateral geniculate complex. *Vis Neurosci* **34**, E012.

Morgan JL, Berger DR, Wetzel AW & Lichtman JW (2016). The fuzzy logic of network connectivity in mouse visual thalamus. *Cell* **165**, 192–206.

Morimoto-Tomita M, Zhang W, Straub C, Cho CH, Kim KS, Howe JR & Tomita S (2009). Autoinactivation of neuronal AMPA receptors via glutamate-regulated TARP interaction. *Neuron* **61**, 101–112.

Mosbacher J, Schoepfer R, Monyer H, Burnashev N, Seeburg PH & Ruppersberg JP (1994). A molecular determinant for submillisecond desensitization in glutamate receptors. *Science* **266**, 1059–1062.

Otis T, Zhang S & Trussell LO (1996). Direct measurement of AMPA receptor desensitization induced by glutamatergic synaptic transmission. *J Neurosci* **16**, 7496–7504.

Priel A, Kolleker A, Ayalon G, Gillor M, Osten P & Stern-Bach Y (2005). Stargazin reduces desensitization and slows deactivation of the AMPA-type glutamate receptors. *J Neurosci* **25**, 2682–2686.

Rafols JA & Valverde F (1973). The structure of the dorsal lateral geniculate nucleus in the mouse. A Golgi and electron microscopic study. *J Comp Neurol* **150**, 303–331.

Rathbun DL, Warland DK & Usrey WM (2010). Spike timing and information transmission at retinogeniculate synapses. *J Neurosci* **30**, 13558–13566.

Renden R, Taschenberger H, Puente N, Rusakov DA, Duvoisin R, Wang LY, Lehre KP & von Gersdorff H (2005). Glutamate transporter studies reveal the pruning of metabotropic glutamate receptors and absence of AMPA receptor desensitization at mature calyx of Held synapses. *J Neurosci* **25**, 8482–8497.

Rossi DJ, Alford S, Mugnaini E & Slater NT (1995). Properties of transmission at a giant glutamatergic synapse in cerebellum: the mossy fiber-unipolar brush cell synapse. *J Neurophysiol* **74**, 24–42.

Rusakov DA & Kullmann DM (1998). Extrasynaptic glutamate diffusion in the hippocampus: ultrastructural constraints, uptake, and receptor activation. *J Neurosci* **18**, 3158–3170.

Rusakov DA, Kullmann DM & Stewart MG (1999). Hippocampal synapses: do they talk to their neighbours? *Trends Neurosci* **22**, 382–388.

Sagdullaev BT & McCall MA (2005). Stimulus size and intensity alter fundamental receptive-field properties of mouse retinal ganglion cells in vivo. *Vis Neurosci* **22**, 649–659.

Sarantis M, Ballerini L, Miller B, Silver RA, Edwards M & Attwell D (1993). Glutamate uptake from the synaptic cleft does not shape the decay of the non-NMDA component of the synaptic current. *Neuron* **11**, 541–549.

Satzler K, Sohl LF, Bollmann JH, Borst JG, Frotscher M, Sakmann B & Lubke JH (2002). Three-dimensional reconstruction of a calyx of Held and its postsynaptic principal neuron in the medial nucleus of the trapezoid body. *J Neurosci* **22**, 10567–10579.

Schwenk J, Baehrens D, Haupt A, Bildl W, Boudkkazi S, Roeper J, Fakler B & Schulte U (2014). Regional diversity and developmental dynamics of the AMPA-receptor proteome in the mammalian brain. *Neuron* **84**, 41–54.

Schwenk J, Harmel N, Brechet A, Zolles G, Berkefeld H, Muller CS, Bildl W, Baehrens D, Huber B, Kulik A, Klocker N, Schulte U & Fakler B (2012). High-resolution proteomics unravel architecture and molecular diversity of native AMPA receptor complexes. *Neuron* **74**, 621–633.

Schwenk J, Harmel N, Zolles G, Bildl W, Kulik A, Heimrich B, Chisaka O, Jonas P, Schulte U, Fakler B & Klocker N (2009). Functional proteomics identify cornichon proteins as auxiliary subunits of AMPA receptors. *Science* **323**, 1313–1319.

Shanks NF, Savas JN, Maruo T, Cais O, Hirao A, Oe S, Ghosh A, Noda Y, Greger IH, Yates JR 3rd & Nakagawa T (2012). Differences in AMPA and kainate receptor interactomes facilitate identification of AMPA receptor auxiliary subunit GSG1L. *Cell Rep* **1**, 590–598.

Sincich LC, Adams DL, Economides JR & Horton JC (2007). Transmission of spike trains at the retinogeniculate synapse. *J Neurosci* **27**, 2683–2692.

Soto D, Coombs ID, Renzi M, Zonouzi M, Farrant M & Cull-Candy SG (2009). Selective regulation of long-form calcium-permeable AMPA receptors by an atypical TARP, gamma-5. *Nat Neurosci* **12**, 277–285.

Taschenberger H, Leao RM, Rowland KC, Spirou GA & von Gersdorff H (2002). Optimizing synaptic architecture and efficiency for high-frequency transmission. *Neuron* **36**, 1127–1143.

Tomita S, Adesnik H, Sekiguchi M, Zhang W, Wada K, Howe JR, Nicoll RA & Bredt DS (2005). Stargazin modulates AMPA receptor gating and trafficking by distinct domains. *Nature* **435**, 1052–1058.

Tomita S, Chen L, Kawasaki Y, Petralia RS, Wenthold RJ, Nicoll RA & Bredt DS (2003). Functional studies and distribution define a family of transmembrane AMPA receptor regulatory proteins. *J Cell Biol* **161**, 805–816.

Tomita S, Fukata M, Nicoll RA & Bredt DS (2004). Dynamic interaction of stargazin-like TARPs with cycling AMPA receptors at synapses. *Science* **303**, 1508–1511.

Traynelis SF, Wollmuth LP, McBain CJ, Menniti FS, Vance KM, Ogden KK, Hansen KB, Yuan H, Myers SJ & Dingledine R (2010). Glutamate receptor ion channels: structure, regulation, and function. *Pharmacol Rev* **62**, 405–496.

Trussell LO, Zhang S & Raman IM (1993). Desensitization of AMPA receptors upon multiquantal neurotransmitter release. *Neuron* **10**, 1185–1196.

Turetsky D, Garringer E & Patneau DK (2005). Stargazin modulates native AMPA receptor functional properties by two distinct mechanisms. *J Neurosci* **25**, 7438–7448.

Turner JP & Salt TE (1998). Characterization of sensory and corticothalamic excitatory inputs to rat thalamocortical neurones in vitro. *J Physiol* **510**, 829–843.

Usrey WM, Reppas JB & Reid RC (1998). Paired-spike interactions and synaptic efficacy of retinal inputs to the thalamus. *Nature* **395**, 384–387.

Vandenberghe W, Nicoll RA & Bredt DS (2005). Stargazin is an AMPA receptor auxiliary subunit. *Proc Natl Acad Sci U S A* **102**, 485–490.

Verdoorn TA, Burnashev N, Monyer H, Seeburg PH & Sakmann B (1991). Structural determinants of ion flow through recombinant glutamate receptor channels. *Science* **252**, 1715–1718.

von Engelhardt J (2019). AMPA receptor auxiliary proteins of the CKAMP family. *Int J Mol Sci* **20**, 1460.

von Engelhardt J, Mack V, Sprengel R, Kavenstock N, Li KW, Stern-Bach Y, Smit AB, Seeburg PH & Monyer H (2010). CKAMP44: a brain-specific protein attenuating short-term synaptic plasticity in the dentate gyrus. *Science* **327**, 1518–1522.

Weyand TG (2007). Retinogeniculate transmission in wakefulness. *J Neurophysiol* **98**, 769–785.

Zeck GM & Masland RH (2007). Spike train signatures of retinal ganglion cell types. *Eur J Neurosci* **26**, 367–380.

Additional information

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

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