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...
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, feedforward 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; 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 interpulse intervals of 10 ms (Turner & Salt, 1998; Chen & Regehr, 2000; Hauser et al., 2014; Chen et al., 2018, 2019).
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 Ca2+ 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 Ca2+, which can be explained by multivesicular release at 2 mM extracellular Ca2+ (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.
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...
relaxation in native AMPA receptor complexes of dLGN neurons (Lein 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). 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). These proteins influence forward trafficking, subcellular localization and importantly gating kinetics 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. TARP γ-2 is the only auxiliary subunit that is expressed at the dLGN relay neuron complex of dLGN neurons. 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 (τ_recovery: wild type = 323 ms, CKAMP44−/− = 66 ms) (Chen et al. 2018). The influence of TARP γ-2 on AMPA receptors contributes to homeostatic plasticity and is involved in the developmental refinement of retinogeniculate synapse function (Louro et al. 2014). Interestingly, the rectification of EPSCs in retinogeniculate synapses is reduced in TARP γ-2−/− mice (Louro et al. 2014), indicating that TARP γ-2 increases preferentially the number of GluA2-lacking Ca2+-permeable AMPA receptors in retinogeniculate synapses. In addition, the influence of TARP γ-2 on AMPA receptors depends on the AMPA receptor subunit (Louro 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 (Louro 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 CNIIH-2 on gating properties, which depends not only on the AMPA receptor subunit but also on the presence of TARPs. CNIIH-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.
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 amplitude of such a signal could desensitize AMPA receptors at non-active synapses. In contrast, 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 (Fig. 3E) do not desensitize from spillover of glutamate from neighbouring active synapse.

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; Isaacman & 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, ∼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 cortogeniculate synapses act as high pass filters (Granseth, 2004). Thus, depolarization and firing frequency 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. 4B). Of note, currents that are mediated by NMDA receptors in retinogeniculate synapses contribute substantially to the depolarization of relay neurons. Due to the Mg2+-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; Augustinaité & 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 Mg2+-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 $\sim 10$ action potentials of retinal ganglion cells (Chen et al. 2018) (Fig. 4A). 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 retinogeniculate synapse function and dLGN neuron firing rates](image)

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 retinogeniculate 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.

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Additional information

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The author declares no competing financial interests.

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Sole author.

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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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