SYMPOSIUM REVIEW

Slow excitatory synaptic currents generated by AMPA receptors

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[Correction made on 15 January 2022, after first online publication: The article has been updated to include the in-text citations of Table 1]

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Abstract  Decades of literature indicate that the AMPA-type glutamate receptor is among the fastest acting of all neurotransmitter receptors. These receptors are located at excitatory synapses, and conventional wisdom says that they activate in hundreds of microseconds, deactivate in milliseconds due to their low affinity for glutamate and also desensitize profoundly. These properties circumscribe AMPA receptor activation in both space and time. However, accumulating evidence shows that AMPA receptors can also activate with slow, indefatigable responses. They do so through interactions with auxiliary subunits that are able promote a switch to a high open probability, high-conductance ‘superactive’ mode. In this review, we show that any assumption that this phenomenon is limited to heterologous expression is false and rather that slow AMPA currents have been widely and repeatedly observed throughout the nervous system. Hallmarks of the superactive mode are a lack of desensitization, resistance to competitive antagonists and a current decay that outlives free glutamate by hundreds of milliseconds. Because the switch to the superactive mode is triggered by activation, AMPA receptors can generate accumulating ‘pedestal’ currents in response to repetitive stimulation, constituting a postsynaptic mechanism for short-term potentiation in the range 5–100 Hz. Further, slow AMPA currents span ‘cognitive’ time intervals in the 100 ms range (theta rhythms), of particular interest for hippocampal function, where slow AMPA currents are widely expressed in a synapse-specific manner. Here, we outline the implications that slow AMPA receptors have for excitatory synaptic transmission and computation in the nervous system.

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Abstract figure legend  Besides their classical fast responses that depress with repeated stimulation (blue), some forms of AMPA-type glutamate receptors can produce a current with slow kinetics approaching 0.5 s. A progressive increase in the current (‘pedestal’, orange) produces short-term potentiation from a postsynaptic locus. Currents generated by slow AMPA receptors have been reported in several regions of the rodent brain; the breadth of their distribution in the rest of the brain remains to be determined. Activity-dependent slow AMPA currents with subcellular expression have broad implications for neuronal computation and synaptic diversity.

Glutamate receptors and excitatory neurotransmission

The neurotransmitter glutamate activates several classes of receptors, which in turn depolarize their host neurons or trigger other signalling pathways. Overall, glutamate receptors expressed in the brain can activate over a range of different epochs (or time constants) from hundreds of microseconds to minutes. Coupling to cellular mechanisms by which the strength of neurotransmission can be changed, lasting from minutes to presumably years, means that glutamatergic neurotransmission can respond to, and act in phase with, almost any signal the brain is likely to encounter. Aside from the rapid AMPA receptor responses, which with their millisecond timing mirror the fast kinetics of the sodium channels that underlie action potentials, other types of glutamate receptor act more slowly. EPSCs that approach 1 s in duration have several well-studied sources. For example, the NR2D subunits confer very slow deactivation on NMDA currents in certain brain regions (Misra et al. 2000; Hildebrand et al. 2014). Kainate receptors can produce very long decay times (Kidd & Isaac, 1999), allowing activity to sum up over time (Castillo et al. 1997; Vignes & Collingridge, 1997). Recently, orphan delta subunits were shown to be essential for slow depolarizing currents in the dorsal raphe nucleus (Gantz et al. 2020). Metabotropic glutamate receptors alter excitability even more slowly, largely through intracellular cascades (Gerber et al. 2007), and their activation may even hyperpolarize their target cells through coupling to potassium conductances (Balmer et al. 2021). In this review, we summarize the evidence and future perspectives for an additional class of slow glutamate response, coming from AMPA receptors.

Biophysics of slow AMPA receptors

Early work using fast agonist perfusion on AMPA receptors presented a coherent picture of fast activation. Whether the preparation was recombinant receptors, those in primary hippocampal cultures or those extracted from the dendrites of principal cells in acute brain
slices, outside-out patch recordings gave responses to glutamate exposure that were fast activating, but that also desensitized rapidly and completely (Colquhoun et al. 1992; Patneau et al. 1993; Mosbacher et al. 1994) (Table 1). These currents broadly matched the fast component of the excitatory synaptic current in the presence of D-2-amino-5-phosphonovaleric acid (APV) (Hestrin et al. 1990). Later, observations of AMPA receptor activation in conditions where auxiliary proteins dominated revealed steady-state activation (Priel et al. 2005), and also slow time components (Tomita et al. 2005). Modal gating, by which a single receptor undergoes reversible changes in gating behaviour (usually a change in open probability) has been described for NMDA receptors (Popescu & Auerbach, 2003) and influences the NMDA receptor gating behaviour (usually a change in open probability) as well as anything that requires desensitization first is unlikely to be seen in non-pathological conditions. However, the slow current is not related to desensitization, but rather in the absence of desensitization, it is much bigger (Carbone & Plested, 2016). Indeed, the slow current also appears indefatigable: it does not sag, at least over the timescale of 5–10 s. Kinetic modelling predicted that the resurgent current is a positive feedback mechanism. The lack of dependence on desensitization advanced the potential relevance of the slow current for basal neurotransmission. Positive feedback means that the magnitude of the resurgent current should grow with stimulation, allowing it to report past activity over a much longer time window than a conventional fast AMPA current. Although desensitization also has the potential to report previous activity over intervals in the 100 ms range, it does so in the manner of negative feedback—the greater the preceding activity, the greater the absence of neurotransmission, because more receptors are locked into inactive states. We named this positive feedback mechanism ‘superactivation’, because it generates AMPA receptors with much higher activity than in their basal state. Further evidence that superactivation involves TARPed AMPA receptors and a modification of their canonical fast gating came from the molecular mechanism, which involves coordination of the extracellular loops of TARPs and the linkers from the glutamate binding domains to the channel pore (Riva et al. 2017). The slow resurgent current is particularly strong with γ-8, suggesting a hippocampal connection because of the selective expression of this subunit.

The characterization of AMPA receptor superactivation in cell lines, as well as in whole-cell patch recordings from neurons (Kato et al. 2010), provided a strong motivation to ask whether slow AMPA currents are seen at synapses in the brain. The prevailing view was that such a current should be obvious, and that many thousands of recordings had failed to reveal it. However, is it true that the slow AMPA current has not been seen at all? On the contrary, far from being absent, the slow current is seen in published work. A facile observation is that baseline current drift during repetitive stimulation is always ignored, but is often in the inward-current direction. More recently investigators explicitly investigated slow AMPA currents (Stinic & Frerking, 2015; Devi et al. 2016; Lu et al. 2017). However, in some other papers, slow AMPA currents are displayed without comment.

Evidence for slow AMPA receptors in brain

What are the telltale signs of slow AMPA receptors in the brain? The search begins with atypical AMPA receptor responses to the competitive AMPA receptor antagonist CNQX (6-cyano-7-nitroquinoxaline-2,3-dione). McBain et al. (1992), with the advantage of studying inhibitory currents, found an effect of CNQX to increase spontaneous IPSC (sIPSC) frequency, and to drive a slow inward current in interneurons. A more potent antagonist

| Table 1. Comparison between the properties of canonical and pedestal AMPA receptors (AMPARs) |
| Classification | Canonical fast AMPARs | Slow pedestal AMPARs |
|----------------|-----------------------|---------------------|
| Activation     | ~1 ms                 | ~100 ms*            |
| Decay          | ~5 ms                 | ~500 ms*            |
| Glutamate affinity | Low                  | High                |
| Desensitization | 0.95%                 | ~0%                 |
| CNQX           | Antagonist            | Agonist             |
| NBQX           | Antagonist            | Relatively inactive*|

Properties of slow AMPA receptors denoted with an asterisk are from Pampaloni et al. (2021). A high affinity for glutamate is inferred from the slow decay. Desensitization properties and affinity for glutamate are inferred from Carbone & Plested (2016). The agonist property of CNQX is inferred from Menuz et al. (2007).
acting at the same site, NBQX (2,3-dioxo-6-nitro-7-sulfamoylbenzo[f]quinoxaline), failed to increase frequency, but DNQX (6,7-dinitroquinoxaline-2,3-dione; another antagonist in the same family) did not change the CNQX effect. The authors took this to indicate that CNQX and DNQX were working through separate pathways, but a neutral effect of DNQX could also be envisaged. Expanding on this observation, Brickley et al. (2001) showed that CNQX, DNQX and NBQX could all increase the frequency of sIPSCs in the cerebellum, but the non-competitive antagonist GYKI-52466 could not. The authors quite correctly stated that the action of quinoxaline diones in this instance was not to block AMPA receptors, but they did not realize that they were thinking of the correct target but the wrong principle. The quinoxaline diones were probably acting as weak activators of AMPA receptor complexes that could generate slow non-desensitizing responses. Observing complex effects of CNQX on CA1 interneurons in the developing hippocampus, Maccarferri & Dingledine (2002) noted presciently that:

“Glutamate receptors are known to interact with many accessory proteins [...] therefore it cannot be excluded that allosteric modulation [...] can prime native receptors towards a state that is sensitive to CNQX activation.”

CNQX and NBQX were also shown to potentiate the steady-state currents activated by glutamatergic agonists in cultures of hippocampal or ventral tegmental neurons (Bijak et al. 1991; Rammes et al. 1998). This observation is perhaps now better understood as the propensity of receptors incorporating TARPs to open when partly occupied by an agonist (Coombs et al. 2017). In heterologous expression, the propensity of Stargazin to confer resistance to inhibition by quinoxaline diones was noted (Cokić & Stein, 2008; MacLean et al. 2014; Devi et al. 2016). Menuz et al. (2007) showed that the effect on QX antagonists was not resistance, but in fact a switch from competitive antagonist to partial agonist. The conversion of CNQX pharmacology extends to various neuronal types, including Purkinje and Golgi cells in the cerebellum and dentate granule cells. However, to get robust activation by CNQX and DNQX, the blocker of desensitization trichloromethazide (TCM) was included. Therefore, although quinoxaline diones can activate AMPA receptors in some neuronal populations, the consequence of this observation for normal brain function was unclear.

Unexpected interactions with presumed antagonists confound experiments but have little meaning for physiology. Aside from these observations, very slow currents that fit the profile of superactive AMPA receptors in complex with auxiliary proteins with very long bursts (Zhang et al. 2014) are also reported at certain synapses. At the cerebellar mossy fibre to unipolar brush cell synapse, an extremely long current decay, inhibited by CNQX but insensitive to Mg2+ (and therefore not NMDA) was reported (Rossi et al. 1995). This decay was extended by blocking AMPA receptor desensitization with cyclothiazide and therefore was due to AMPA not kainate receptors. Purkinje cell stimulation has a very slow component that is resistant to NBQX (Devi et al. 2016) but does show some pentobarbital inhibition, overlapping with the pharmacology of recombinant AMPA receptors with Stargazin. Striking evidence of AMPA-mediated slow currents, including a very slow decay, was reported also in the rat inferior colliculus (Wu et al. 2004). The slow clearance of glutamate by transporters, combined with Stargazin, allows a slow AMPA receptor-mediated response (Lu et al. 2017) and slow AMPA channels also contribute to long miniature currents (Balmer et al. 2021). This mechanism is presumably similar to the recovery of GABA receptors from desensitization through the open state (Jones & Westbrook, 1995).

In other reports, slow AMPA currents are probably present but not described (Fig. 1). Recording in CA1 interneurons, and using normal magnesium (which should substantially block any NMDA receptors), the Schaffer input was much more facilitating than the alveus input (Wierenga & Wadman, 2003). Their study does not mention the large and slowly developing steady-state current that is obtained (see Fig. 1). Similar responses were obtained from pyramidal cells, but are not plotted. Comparing striatum and hippocampus, Lape & Dani (2004) noted a strong steady-state current with stimulation in striatum. In the report, however, the slow current was not observed in CA1. Also in CA1 pyramidal cells, very slow decays after burst input are reported, and these are altered by NMDA antagonists, but never entirely blocked (Lozovaya et al. 2004). Similarly, accumulating currents from burst stimulation in CA1 dendrites were reduced by NMDA and calcium channel block, but not abolished (Remy & Spruston, 2007). Quite reasonably, the latter study concludes that both NMDA receptors and calcium channels are involved. Such logic entails an important distinction between sensitivity (denoting involvement) and complete and selective block (denoting mechanistic responsibility). The presence of other slow currents is not excluded, when inhibition of the response is incomplete. In many similar studies, experiments were done in NBQX, with the intention of blocking AMPA and kainate receptors. However, as we outline below, resistance to NBQX is a key property of slow AMPA currents.

At some synapses with high release rates, tail currents much slower than the fast initial activation of AMPA receptors can develop at the end of rapid stimulation (Saviane & Silver, 2006). This current outlives vesicular release, and therefore probably corresponds to slow AMPA receptors. At the ribbon synapse in vestibular
calices, very slow decays are observed at a fraction of sites (Sadeghi et al. 2014). Blocking uptake with TBOA (threo-beta-benzyloxyaspartate) has only a small effect. Such responses could be from kainate receptors, but in the spiral ganglia, the first auditory synapse after the inner hair cell, slow AMPA responses are definitively seen. Responses sensitive to cyclothiazide and with a large kainate response show hallmarks of TARPed AMPA receptors, and give large steady-state currents that also wash out slowly (Ruel et al. 1999). Interpretation of slow postsynaptic currents at ribbons is confounded by steady, phasic release (Jackman et al. 2009). In some cases, postsynaptic currents with a steady-state component are very accurately described as a simple summation of brief miniature EPSCs (mEPSCs), and correspond purely to vesicular release (Oesch & Diamond, 2011).

Overall, the concepts outlined above have largely remained separate from each other. Recently, we have examined slow AMPA receptors in the hippocampus systematically. Slow AMPA receptors, with kinetics >100 ms, defined by GYKI 52466 inhibition (Table 1) and sensitivity to auxiliary subunit perturbation (Fig. 2), are widespread in principal cells, with a mosaic distribution (Pampaloni et al. 2021). Non-desensitizing AMPA responses accumulate with repetitive stimulation in CA1 pyramidal cells, and to a lesser extent in CA3. Repetitive stimulation at as low as 5 Hz can generate long-lived depolarization, and the magnitude of the slow current is frequency-dependent (Pampaloni et al. 2021) as observed in other cases (Wu et al. 2004; Combe et al. 2018).

### The pharmacology and composition of AMPA receptor complexes

As discussed above, TARPs confer NBQX resistance, and convert CNQX and DNQX into partial agonists. It is as yet unclear whether other auxiliary subunits can also provide resistance to NBQX, or alter inhibitor

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**Figure 1. Examples of slow AMPA synaptic currents in the brain**

Slow developing ‘pedestal’ currents in normal magnesium with Schaffer collateral stimulation (Wierenga & Wadman, 2003). A slow decaying AMPA current that is developmentally regulated is found in hippocampal interneurons (Stincic & Frerking, 2015). A large steady-state response (and very slow decay) develops with higher frequency stimulation in the inferior colliculus (Wu et al. 2004). In the cerebellum, unipolar brush cells have a slow rebound current (Lu et al. 2017), and a subsaturating concentration of NBQX (200 nM) spares the slow AMPA current that develops with train stimulation in the cerebellar Purkinje cell (Devi et al. 2016). A large steady-state response (and very slow decay) develops with higher frequency stimulation in the Inferior Colliculus (Wu et al. 2004); Copyright 2004 Society for Neuroscience.
pharmacology in other ways. However, both canonical rapid AMPA currents and the slow pedestal component are abolished by non-competitive antagonists such as GYKI-52466 (Pampaloni et al. 2021). The disadvantage of non-competitive antagonists is their lower potency, probably due to the dynamic nature of their binding site in the transmembrane linkers (Yelshanskaya et al. 2016). No specific blocker of the slow AMPA current has been identified so far, although pentobarbital was shown to reduce the slow component of the parallel fibre to Purkinje cell synaptic current (Devi et al. 2016). Another tantalizing possibility for selective inhibition comes from forebrain specific blockers that target complexes with γ-8 (Kato et al. 2016; Maher et al. 2016). These drugs block super-activation (also called resensitization) in recombinant A2-γ-8 receptors (Dohrke et al. 2020). Notably, despite

![Figure 2](image-url)

**Figure 2. Slow AMPA receptors in the hippocampus and in heterologous expression**

A, uncaging 4-Methoxy-7-nitroindolyl-glutamate (MNI-glutamate) at 10 Hz reveals a mosaic distribution of slow, accumulating pedestal responses (marked with magenta box in each panel) in CA1 pyramidal cells in the hippocampus (Pampaloni et al. 2021). B, heteromeric AMPA receptors in complex with γ-8 allow slow responses resistant to inhibition by NBQX. C, repetitive stimulation of recombinant receptors in complex with γ-8 (20 Hz) produces a slow accumulation of the current (modified from Carbone & Plested, 2016). D, mosaic expression of pedestal responses to MNI-glutamate uncaging is converted to be near-universal following overexpression of γ-8. A, B and D are modified from Pampaloni et al. (2021).
being quite selective, these drugs also block currents in the cortex (Kato et al. 2016), indicating a wider role for \( \gamma^-8 \). No single auxiliary protein can fully recapitulate the slow AMPA phenotype. Stargazin is a weak modulator of gating, and has an ‘instant’ action with very limited resurgent current (Carbone & Plested, 2016; Pampaloni et al. 2021). On the other hand, \( \gamma^-8 \) modulates gating more strongly but over a longer time interval. Overall, specific blockers may be difficult to obtain if the slow AMPA current is a more general property of multiple species of AMPA receptor complex composed of different auxiliary proteins.

What auxiliary subunits are most likely to participate in slow AMPA currents? Because of their observed slow kinetics in heterologous expression, \( \gamma^-8 \), \( \gamma^-4 \) and CNIH2 seem the most obvious choices. CNIH2 was convincingly shown to contribute to the slowed decay of AMPA receptors in some interneurons (Boudkkazi et al. 2014). Even though \( \gamma^-8 \) is highly expressed in the hippocampus, its expression in principal cells is probably not saturated. Overexpression converted all connections in all cells to have slow currents and slowed mEPSCs (Pampaloni et al. 2021). This means that \( \gamma^-8 \) might indeed be expressed at a low level in some cells (where the pedestal component is absent) and at higher (but not saturating) levels in others. In the dentate gyrus (DG) granule cells, CKAMP44, a strong negative modulator of gating via its stabilization of desensitization, is well expressed (Khodosevich et al. 2014) and might play a dominant role because pedestal currents are entirely absent and current decays are fast (Pampaloni et al. 2021). Deletion of CKAMP44 in the dorsal lateral geniculate nucleus leads to a large pedestal response (Chen et al., 2018). Along the same lines, the speeding of kinetics by GSG1L may also play a role in generating AMPA receptor diversity in the hippocampus (Gu et al. 2016).

Structures with \( \gamma^-8 \) reveal preferential locations for interaction (Herguedas et al. 2019) with a 4:2 stoichiometry. Stoichiometry determines gating (Shi et al. 2009; Hastie et al. 2013; Miguez-Cabello et al. 2020) and so we should expect that the activation of complexes will vary with composition. Notable here is that the pedestal current appears with repetitive activity, and vanishes after inactivity. For receptors in complex with TARPs at least, glutamate can activate receptors with almost the same kinetics as receptors without TARPs, the canonical fast mode. Auxiliary proteins allow a mode switch, rather than determining a slow single activation mode. Deletion of Stargazin in the cerebellum altered but did not ablate slow responses evoked by 100 Hz trains (Lu et al. 2017), providing further evidence for the participation of multiple auxiliary proteins. At least four major types of AMPA receptor are present in the hippocampus. These types are potentially switchable and dynamic in time, and give hippocampal synapses a broad palette of kinetic profiles:

1. fast principal cell type, 10–20 ms decay (DG and pyramidal cells) (Geiger et al. 1995; Pampaloni et al. 2021; Zhang et al. 2021);
2. pyramidal pedestal type, 500 ms decay (Pampaloni et al. 2021);
3. fast interneuron type (with GluA4, less or no GluA2) (Sambandan et al. 2010); and
4. slow interneuron type (including CNIH2) (Boudkkazi et al. 2014).

Previously, mass spectrometric analysis suggested proximal and distal interactions between AMPA receptors and their auxiliary subunits (Schwenk et al. 2012, 2014). However, the complexity of individual hippocampal receptors is now becoming clear. Hetero-decameric complexes purified directly from the brain indicate unexpectedly broad potential for gating modulation (Yu et al. 2021) (Fig. 3). Complexes with multiple auxiliary proteins were also resolved in an open state, confirming that such ‘loaded’ complexes gate normally (Zhang et al. 2021). The core subunits (GluA1–4) combine with three distinct auxiliary proteins at three different slots, increasing the possible combinations to a bewildering extent. This work also indicates that auxiliary proteins can physiologically interact with each other (SynDIG4 and CNIH2). At the primary site (occupied in all structures with auxiliary proteins to date regardless of stoichiometry), GSG1L and TARPs are reported, giving a minimum of six options. At the

Figure 3. Auxiliary proteins in a native receptor purified from hippocampus

A, side view of the AMPA receptor complex in the membrane. The complex was purified on the GluA2 subunit (which occupies the B/D positions). The identity of the GluA subunit in the A/C sites is unclear in this model. B, plan view; section through the membrane domains shows that auxiliary proteins are found at three distinct sites. Redrawn from Yu et al. (2021).
second site, CNIH2/3 and TARPs, or no auxiliary subunit at all, gives seven options. The presence or absence of SynDIG4 at the third site gives two options. Across the six docking sites per receptor, this gives $\sim 7000 \ (6 \times 6 \times 7 \times 7 \times 2 \times 2)$ combinations, without considering the different combinations of core GluA1–4 subunits. The assumption of independence in this estimate is probably not met. Most of these combinations will not be found in vivo, due to cell-type- and region-specific expression (Schwenk et al. 2014). There is also some GluA1–4 subunit specificity of auxiliary protein associations in the native context (Herring et al. 2013). Figure 4 summarizes the mixed complexes demonstrated to date by functional measurements and/or structural studies.

A further note of caution is that the cellular abundance of a modulatory protein may not correspond to participation in synaptic transmission. Paradoxically, changes in receptor abundance with long-term potentiation are typically quite small when measured biochemically (about 50% increase) whereas responses increase by 200% in a typical experiment. Some abundant auxiliary proteins are mainly if not entirely intracellular (Schwenk et al. 2019). There is a large pool of extrasynaptic receptors, and the difference between imaging only surface receptors and all receptors indicates that there is also a large pool of endoplasmic reticulum-resident complexes. The fraction that diffuses into synapses may be a minor one, and therefore low-abundance auxiliary proteins that cause large gating changes may be difficult to detect by traditional biochemical or imaging means.

A range of cellular processes have been coupled to AMPA receptor trafficking, including binding proteins such as PICK1 (Citri et al. 2010) and adaptors such as AP2 (Lee et al. 2002) that could in principle alter gating properties. The same might be true of extracellular interactions with trans-synaptic proteins. However, in the cases where it was measured, kinetic effects of binding scaffold proteins or covalent modification were limited (Derkach et al. 1999; Fu et al. 2003) with phosphorylation principally altering single channel conductance (Kristensen et al. 2011).

Interaction with glutamate spillover and transport

Glutamate transporters (excitatory amino acid transporters, EAATs) rapidly remove glutamate from the synaptic cleft, which shortens the decay phase of glutamatergic currents. The effect is most marked on NMDA receptors but the buffering action is fast enough to speed up fast AMPA receptor decays (Diamond &

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**Figure 4. The scope of auxiliary proteins in the hippocampus**

Six prototype auxiliary currents are shown. Binary and ternary combinations are demonstrated from physiology and/or structural studies. Complexes are ranked (from left to right) according to their approximate expected effect on the synaptic response. Membrane topologies are indicated; the topology of SynDIG4 remains unclear. Confirmed and putative arrangements of subunits of increasing complexity are shown (core subunits GluA1-4 as black/grey squares). With between two and seven possible choices for each of the six positions, in principle $\sim 7000$ combinations are conceivable from known partners. However, selective expression and redundancy will probably limit diversity to around 10–100 detectable combinations. Experimental evidence for multiple auxiliary protein incorporation is as follows: AK10 (Kato et al. 2010), MG12 (Gill et al. 2012), KK14 (Khodosevich et al. 2014), XG16 (Gu et al. 2016), LM18 (Matt et al. 2018), JY21(Yu et al. 2021).
AMPAR receptor kinetics can also slow down transiently during development (Schmidt-Salzmann et al. 2014). An important observation in favour of multiple contributions to the slow current at specific cerebellar synapses (Lu et al. 2017) is that the effects of a positive allosteric modulator of AMPAR receptors and of transporter blockade sum up. Therefore, both of these distinct mechanisms could contribute to the same functional phenotype of a slow EPSC decay (Overstreet et al. 1999).

A place and space for slow AMPAR receptors?

From the point of view of membrane biophysics, the slow AMPAR current represents an interesting ramification of receptor function. Aside from this, it is essential to define and test the roles that slow AMPAR receptors might play in the brain. What are the potential advantages or disadvantages for neurons of this previously unsuspected indefatigable slow current? The known slow excitatory currents in the brain provide some guidance.

The kainate receptor current at the mossy fibre synapse (Castillo et al. 1997; Vignes & Collingridge, 1997) contributes to the detonator property of this input to dominate the firing of CA3 pyramidal cells (Henze et al. 2002; Sachidhanandam et al. 2009). It appears that the slow AMPAR current can play a similar role in CA1 (Pampaloni et al. 2021). Intriguingly, block of the slow accumulating current by the kainate receptor-specific competitive antagonist UBP 310 is incomplete (Pinheiro et al. 2013), reflecting either the inconsistency of the blocker across different kainate receptor subtypes, but also perhaps reflecting a contribution of slow AMPAR receptors in CA3 pyramidal cells (Pampaloni et al. 2021). Slow currents outside the hippocampus may derive from kainate receptors as well. Digby et al. (2017) showed that in layer 3 of the medial entorhinal cortex (MEC), membrane potential up-states in principal cells are sustained and re-established by kainate receptors, with little role for AMPAR receptors. Analysing mostly layer 2 cells, slow currents that develop upon repetitive stimulation from septoentorhinal projections provide a speed signal to pyramidal cells in MEC (Justus et al. 2017), and this current is not due to NMDA receptors. In the anterior cingulate cortex, the pharmacology and genetic ablation of kainate receptors indicate slow currents deriving from both kainate and AMPAR receptors, with magnitudes dependent on stimulation (Wu et al. 2005). Very slow kainate currents were also reported at thalamocortical synapses (Kidd & Isaac, 1999). When incorporated into kainate receptor complexes, Neto subunits can also produce modal gating (Zhang et al. 2014), as TARPS do for AMPAR receptors. Moreover, slow time constants of deactivation and desensitization for kainate receptors in the brain relate directly to NETO subunits.
(Straub et al. 2011). Separating kainate receptors from slow AMPA currents will require careful comparison of UBP 310/302 and GYKI 52466 (or its more potent analogue, GYKI 53655) block, with the caveat that none of these agents is perfectly specific.

NMDA receptors have been assigned a wide range of roles in spanning cognitive time (Lisman, 1999). However, although there is strong evidence for NMDA involvement in slow dendritic excitation and plateau potentials (Palmer et al. 2014), it is curious that the same signal that is essential for plasticity (via the associated calcium input) would also be exclusively used to signal regular excitatory processes that need to last for more than ∼50 ms. Intriguingly, some computational models of NMDA participation treat NMDA receptors as a pure Na+ conductance, potentially overstating excitatory drive whilst also ignoring the obligatory Ca2+ influx, and the downstream effects of Ca2+ (Berteau & Bullock, 2020). NMDA receptor unblock from Mg2+ is also neither instant nor complete at relevant membrane potentials (Kampa et al. 2004). Slow AMPA receptor activation offers another option to produce sustained depolarization (>100 ms) that does not entail much calcium entry (at least in cells expressing GluA2 edited at the Q/R site). In such a scenario, voltage-gated channels could be engaged with a plateau potential, without necessarily triggering plasticity. The caveat in this case is that the depolarization that occurs may trigger plasticity through other pathways, and this will require further investigation.

The time interval of 100 ms accessed by slow AMPA receptors is interesting because in mammals, alpha/theta oscillations in the 10 Hz range are prominent in the activity of neuronal populations (Buzsáki, 2002). The computational meaning of these oscillations remains unclear, but some links to behaviour and memory were demonstrated. For example, the hippocampal formation has been extensively shown to ‘tune’ to different frequencies, both in rodents and in humans, and establish transient long-range connections with other brain structures, depending on the cognitive task to be performed (Buzsaki, 2006; Herweg et al. 2016; Bush et al. 2017). In particular, theta (4–8 Hz) and alpha (9–13 Hz) rhythms are now characterized to coexist in human hippocampus during working memory tasks (Leszczynski et al. 2015). Whether this can be achieved with a static synaptic architecture is unclear. Compared to the addition or removal of, for instance, NMDA receptors which cannot be fast, the mode-switching of AMPA receptor activation gating is complete within a few hundred milliseconds, fast enough to tune to a new input, and detune as required. Such an approach is also scalable over any number of connections (up to thousands as necessary), whereas a solution involving rapid trafficking of ion channels would soon be exhausted. Therefore, the AMPA receptor in complex with auxiliary proteins offers a rare opportunity to exercise a molecular-level positive feedback mechanism (Carbone & Plested, 2016) that is adapted to the rhythms of the hippocampus. Transient association of auxiliary subunits need not be excluded from such a scheme, even if the timescale for such subunit exchange (Tomita et al. 2004) is unknown. Evidence for both naive and complexed AMPA receptors is available (Bats et al. 2012). A future challenge will be to address the dynamics of these associations and the conditions that determine them in physiological contexts.

The heterogeneity of AMPA-mediated responses challenges the classical view of short-term potentiation as a purely presynaptic phenomenon (Fig. 5). Depression due to depletion of vesicles was recognized in the 1970s (Castellucci & Kandel, 1974), and potentiation due to calcium accumulation even earlier (Katz & Miledi, 1968), and these concepts, based in the presynaptic terminal, have dominated thinking on short-term synaptic plasticity ever since. Even though receptor desensitization was recognized already in the 1950s at the neuromuscular junction (Katz & Thesleff, 1957), postsynaptic mechanisms of short-term facilitation are lacking (with the important exception of the mossy fibre-CA3 connection; Castillo et al. 1997; Vignes & Collingridge, 1997; Henze et al. 2002). In this context,
depression due to postsynaptic receptor desensitization and facilitation from the slow accumulating pedestal current offer to balance presynaptic mechanisms, creating a symmetrical framework (Fig. 5). Either neuron involved in a given synaptic connection can determine short-term plasticity in a synapse-specific manner. The extent to which individual neurons regulate postsynaptic sensitivity through AMPA receptor composition remains to be demonstrated, but the mosaic distribution of slow pedestal currents in CA1 pyramidal cells suggests that the raw mechanisms are present.

The observation that slow pedestal currents can be evoked adjacent to classical fast AMPA responses further indicates a clear putative mechanism of synaptic diversity from a post-synaptic locus, as has been shown for interneurons with GluA2 (Tóth & McBain, 1998; Sambandam et al. 2010). In this way, a CA1 pyramidal cell could select between inputs actively, perhaps via trafficking of distinct AMPA receptor complexes on a per-synapse basis, rather than acting as a passive acceptor of inputs, as is usually modelled. If AMPA receptors are driven into superactive states with slow kinetics, miniature currents should develop longer decay times during persistent activity. This point has implications for deconvolution of miniature currents and may lead to overestimates of neurotransmitter release from such analyses.

If the hypothesis that CA1 pyramidal cells compare diverse inputs and switch their firing mode appropriately is correct, modelling shows that a balance of slow currents (beyond 100 ms) is required to do this efficiently (Berteau & Bullock, 2020). Plateau potentials may help pyramidal neurons to solve the credit assignment problem (Richards & Lillicrap, 2019), necessary for efficient learning. Are synapses with slow AMPA receptors opposed by terminals with low release probability? Answering this question will not be easy, but in such a scenario, slow AMPA receptors will respond preferentially to burst input, and may therefore also function in signal multiplexing (Payeur et al. 2020).

Future perspective

Further work is needed to properly determine the prevalence of slow AMPA responses across brain regions. Progress in this regard will depend on comparisons of synaptic AMPA receptor function to subcellular expression, along with subcellular imaging, in identified neurons. However, the diverse observations that we collect here suggest that slow AMPA mediated currents are widely distributed. Despite the shared mechanism, pedestal currents from TARPed AMPA receptors are likely to be exploited differently in various contexts, for example between the hippocampus and cerebellum (Overstreet et al. 1999; Devi et al. 2016; Lu et al. 2017; Pampaloni et al. 2021). The disadvantages of slow AMPA currents are probably substantial, including vulnerability to seizure, and loss of input and timing specificity. For these reasons, slow AMPA currents are probably deployed selectively, both within cellular populations and also between cells. Cells that express slow AMPA currents might have particular adaptations to be resistant to periodic long depolarizations. In CA1 pyramidal cells, accumulating AMPA currents (mostly at higher frequencies) interact with other channels including SK and HCN channels, and also are affected by neurotransmitters such as acetylcholine (Magee, 1999; Combe et al. 2018). Because some dendrites integrate calcium and voltage in distinct ways (Tran-Van-Minh et al. 2016), the coupling to voltage-gated channels, calcium-gated channels and NMDA receptors may be complicated. Calcium entry through AMPA receptors lacking GluA2 can in any case trigger plasticity (Soler-Llavina & Sabatini, 2006; Hainmueller et al. 2014). Two mechanisms (super-activation and desensitization) could regulate short-term plasticity on a subcellular basis through differential AMPA receptor trafficking. These processes in principle allow dynamic reassignment of the weights of synaptic inputs. However, if and when such opportunities are deployed in the context of other plasticity mechanisms remains unknown, and is an obvious area for future investigation.

Are slow receptor responses an evolutionary hangover? It now appears that all glutamate receptor subtypes have the facility to generate slow (seconds) components of excitation. Did all glutamate receptors start out slow, and become faster as an adaptation during brain development? Molecular dynamics simulations of the AMPA receptor binding domains show that pathways over the ligand binding domain speed up glutamate association (Yu et al. 2018). Other adjustments may have accelerated AMPA receptor activation further for specific tasks. Further biophysical work will be needed to define the breadth of mechanisms of auxiliary protein modulation that allow slow AMPA currents, and equally any molecular mechanisms that block them. Overall, the repertoire of AMPA receptor signalling extends far beyond the canonical, monolithic fast gating behaviour, and may yet grow further as other brain regions are investigated at molecular and cellular levels.

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**Additional information**

**Competing interests**

The authors declare no competing interests.

**Author contributions**

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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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