Long-term synaptic plasticity in hippocampal interneurons

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Abstract | Rapid memory formation relies, at least in part, on long-term potentiation (LTP) of excitatory synapses. Inhibitory interneurons of the hippocampus, which are essential for information processing, have recently been found to exhibit not one, but two forms of LTP. One form resembles LTP that occurs in pyramidal neurons, which depends on *N*-methyl-D-aspartate receptors and is triggered by coincident pre- and postsynaptic activity. The other depends on Ca^{2+} influx through glutamate receptors that preferentially open when the postsynaptic neuron is at rest. Here we review these contrasting forms of LTP and describe how they are mirrored by two forms of long-term depression. We further discuss how the remarkable plasticity of glutamatergic synapses on interneurons greatly enhances the computational capacity of the cortical microcircuit.

Long-term potentiation (LTP). The activity-dependent strengthening of synaptic transmission (usually lasting longer than 30 minutes) that is widely thought to underlie certain forms of memory acquisition. LTP is commonly induced by brief, high-frequency (100 Hz) stimulation (tetanization) of presynaptic axons, or by pairing low-frequency (1–2 Hz) presynaptic stimulation with postsynaptic depolarization. LTP at some glutamatergic synapses on interneurons obeys different induction rules.

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Few areas of neuroscience have mobilized as many resources as the hunt for the cellular substrate of memory. This venture has been rewarded with spectacular breakthroughs, in particular the discovery of long-term potentiation (LTP) and the accumulation of overwhelming evidence that *N*-methyl-D-aspartate receptors (NMDA receptors) have a central role in the acquisition and stabilization of spatial memory. LTP and the related phenomenon long-term depression (LTD) are readily elicited in pyramidal neurons, but until recently there has been little evidence that these forms of use-dependent synaptic plasticity also occur in inhibitory interneurons. Although these GABA (γ-aminobutyric acid)-releasing cells are highly heterogeneous (see below), as a group they are generally thought to regulate the overall level of excitability in the network and to contribute to the precise timing of action potentials. As a result of these properties, they have been proposed to provide a relatively unvarying scaffold for computations and for information storage that is mediated by networks of principal cells[1].

Here we suggest that the reputation of interneurons as the unglamorous accountants of the brain is unjustified: excitatory synaptic inputs to many hippocampal interneurons in fact show several forms of long-term use-dependent plasticity, including (but not restricted to) NMDA-receptor-dependent LTP and LTD. At least some of these forms of synaptic plasticity show pathway specificity — that is, they do not spread indiscriminately to other synapses that converge on the same cell. Because interneurons generally do not have profuse dendritic spines, this observation undermines long-held assumptions about the roles of these spines in compartmentalizing synaptic plasticity. Recent work on synaptic plasticity in interneurons has also uncovered a highly unexpected new induction rule for LTP that is diametrically opposite to that seen in pyramidal cells.

These discoveries have shed new light on the roles of the different types of glutamate receptors, and have opened a door on previously unsuspected computational complexity in elemental hippocampal circuits. Nevertheless, there are many apparent inconsistencies in the emerging literature on synaptic plasticity in interneurons, which might stem from the heterogeneity of these neurons and from the diversity of the glutamatergic axons that innervate them. We therefore devote some space to summarizing the salient aspects of these heterogeneities, before considering the evidence for distinct types of use-dependent plasticity, their underlying mechanisms and their computational implications. Although we focus most of this review on synaptic plasticity in hippocampal interneurons, it is highly likely that the emerging principles also apply in the neocortex.

Interneuron diversity

A difficult obstacle to the study of interneurons is their extensive heterogeneity. Interneurons have highly diverse dendritic and axonal projection patterns, pre- and postsynaptic partners, and electrophysiological and immunohistochemical properties. Although major areas of uncertainty remain, a list of cortical interneuron 'types' is emerging. This has been especially successful in the hippocampus: this phylogenetically old part of the cerebral

NMDA receptor
A type of ionotropic glutamate receptor that is characterized by its slow kinetics and strong permeability to calcium. Its name derives from the potent and specific agonist *N*-methyl-D-aspartate.

Long-term depression
The counterpart of LTP. It is defined as an activity-dependent weakening of synaptic strength.

Inhibitory interneuron
A GABA-releasing neuron in the brain that projects mainly to local target neurons.

Principal cell
A type of neuron that usually releases glutamate and that integrates multiple synaptic inputs and sends the resultant information out through axons that project to relatively remote structures. Principal cells account for 80–90% of neurons in the cortex.

Fast-spiking axo-axonic cell
An interneuron that forms characteristic 'cartridge' synapses on the initial segments of axons. They are also known as 'chandelier' cells.

Neurogliaform cell
An interneuron that forms a dense axonal and dendritic plexus. Its shape is reminiscent of that of astrocytic glial cells.

O-LM cell
An inteneuron that has its soma and dendrites in the stratum oriens, and that projects to the stratum lacunosum-moleculare.

Basket cell
An interneuron that innervates the perisomatic region of target neurons. The axonal arborization of basket cells often resembles a basket surrounding the target cell body.

Feedback–feedforward dichotomy
The idea that interneurons mediate either feedback or feedforward inhibition, depending on whether they are innervated by the axons of remote principal cells or by the recurrent collaterals of local principal cells, respectively.

cortex has a simplified laminar structure, which makes it easier to classify hippocampal interneurons according to the location of their cell bodies, axons or dendrites relative to the stereotyped palisade-like arrangement of pyramidal neurons. A comprehensive survey of hippocampal interneurons is beyond the scope of this Review[2,3], but some of the subtypes are relatively easy to recognize, and there is a good consensus about their properties.

Fast-spiking axo-axonic cells (or 'chandelier' cells) project to the axon initial segments of pyramidal neurons, where they form characteristic 'cartridges' — clusters of presynaptic specializations that are orientated perpendicular to the pyramidal cell. Neurogliaform cells in the stratum lacunosum-moleculare in the CA1 region also have relatively stereotyped morphological and electrophysiological properties, as do so-called O-LM cells, which have their cell bodies and dendrites in the stratum oriens and project their axons to the stratum lacunosum-moleculare, where they innervate the apical dendrites of pyramidal neurons. Basket cells are also relatively well characterized, and at least two subtypes are distinguished by their expression of either cholecystokinin (CCK) or parvalbumin and by their firing properties. CCK-positive basket cells also express endocannabinoid CB1 receptors at their terminals. All of these hippocampal interneurons have their counterparts in the neocortex. Other interneurons are less easily identified. Nevertheless, several converging sources of information, including correlations between the expression of neurochemical markers and characteristic firing patterns in response to depolarizing current[4], promote the view that a reasonably complete interneuron taxonomy will soon be agreed on[5].

Spatial and temporal information processing

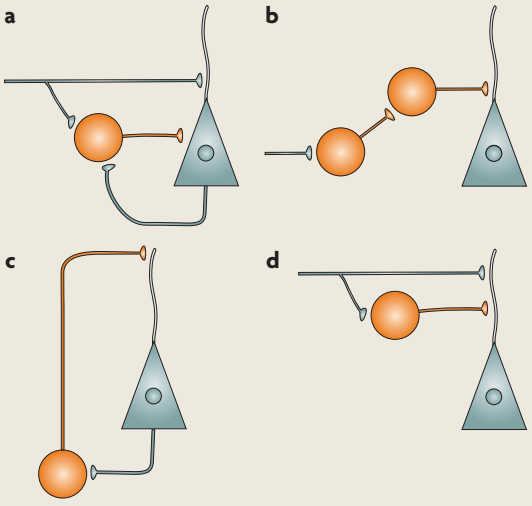
An essential complement to interneuron classification is an understanding of the neurons' roles in information processing (BOX 1). Classically, inhibition has been considered within the framework of a feedback–feedforward dichotomy. This is of limited usefulness when attempting to classify interneurons themselves, because many are innervated by excitatory axons from more than one source. Nevertheless, the two types of inhibition can be distinguished experimentally by evoking action potentials in afferent excitatory axons and monitoring the consequences for the propagation of excitation and inhibition in the network. Such experiments in acute brain slices have shown, for instance, that feedforward inhibition greatly reduces the latency jitter of action potentials in pyramidal neurons and thus allows them to integrate converging information with a high degree of temporal fidelity[6].

The roles of distinct interneurons in shaping the patterns of activity of pyramidal cells depend not only on their anatomy, but also on their intrinsic passive and active electrical properties, their synaptic kinetics and the subcellular domains of the target neurons on which they make GABA-releasing synapses. Thus, dendrite-projecting O-LM cells (BOX 1, panel c) tend to fire at relatively low frequencies (within the theta band (4–8 Hz)), and they have been implicated in the generation of theta oscillations[7]. Perisomatic-projecting basket cells (BOX 1, panel a), by contrast, are implicated in the generation of gamma band (30–70 Hz) oscillations[8]. However, it is likely that the basket cell subtypes have subtly different roles in the circuit: notably, those that express CCK and CB1 endocannabinoid receptors tend to fire more slowly and integrate presynaptic activity over longer time windows than parvalbumin-positive and CB1-receptor-negative basket cells[9].

Another insight into the cell-type specificity of temporal processing comes from *in vivo* recordings of the activity of identified interneurons during different electroencephalographic states. Distinct interneurons were recently shown to fire at characteristic phases of hippocampal theta oscillations and sharp-wave ripples[3,10] — activity patterns that are associated with exploratory activity and consummatory behaviour, respectively. Some of these firing patterns are unexpected. For instance, O-LM cells are silenced during sharp-wave ripples — a time when local pyramidal neurons (which

Box 1 | **Logical operations that are performed by interneurons**

A simplistic classification of interneurons (shown in orange) as either feedback or feedforward has limited value, because many cells (for example, hippocampal basket cells, (**a**)) are excited by both the axon collaterals of local principal cells and by the excitatory axons of more remote structures[9]. Furthermore, some interneurons selectively innervate other interneurons (**b**)[81,91]. Nevertheless, there are some exceptions: O-LM cells seem mainly to mediate feedback inhibition, because they receive most of their excitation from the same population of local pyramidal cells that they innervate (**c**)[92]. Conversely, neurogliaform cells in the stratum lacunosum-moleculare of the CA1 region are excited by extrinsic afferent inputs from the entorhinal cortex and innervate local pyramidal neurons, and so can be thought of as mediating feedforward inhibition (although they also inhibit other neurogliaform cells) (**d**)[93]. Excitatory axons are shown in green; inhibitory axons are shown in orange.



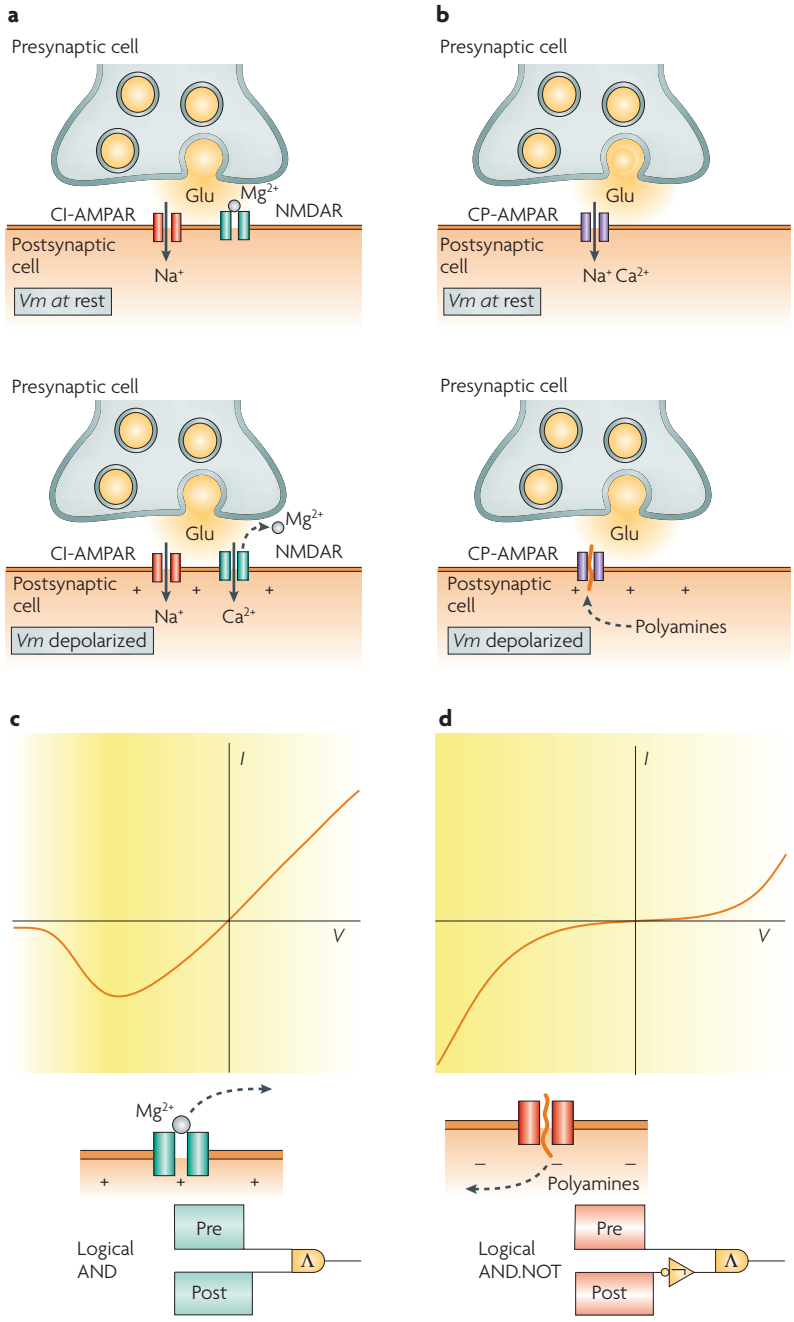


Figure 1 | **The rectification of ionotropic glutamate receptors and Ca^{2+} influx at different types of glutamatergic synapse.** Glutamatergic synapses on interneurons tend to be equipped either with Ca^{2+}-impermeable AMPA receptors (CI-AMPARs) and abundant NMDA receptors (NMDARs) (**a**), or with Ca^{2+}-permeable AMPA receptors (CP-AMPARs) and few NMDARs (**b**). Glutamate-bound NMDARs are blocked by Mg^{2+} ions at resting membrane potentials (**a**, top), but open with depolarization (**a**, bottom). CP-AMPARs, on the other hand, open at negative potentials (**b**, top) but are blocked by intracellular polyamines during depolarization (**b**, bottom). **c**,**d** | The current–voltage (*I*/*V*) relationship. At synapses with NMDA receptors (**c**), Ca^{2+} influx requires postsynaptic depolarization (indicated by yellow shading). At synapses with CP-AMPARs, on the other hand (**d**), Ca^{2+} influx occurs when the membrane is at resting potential or hyperpolarized (indicated by yellow shading). The conditions can be thought of as a logical 'AND' gate for NMDA receptors (Ca^{2+} influx upon pre- *and* postsynaptic activity) (**c**) and a logical 'AND.NOT' gate for CP-AMPARs (Ca^{2+} influx upon pre- *and not* postsynaptic activity) (**d**). These conditions are schematically illustrated by the logical symbols Λ and ¬. AMPA, α-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid; Glu, glutamate; NMDA, *N*-methyl-D-aspartate; *Vm*, membrane potential.

are the main source of excitation driving the O-LM cells) fire intensely. How this silencing comes about remains to be determined, but one possibility is that the O-LM cells are actively inhibited by other interneurons.

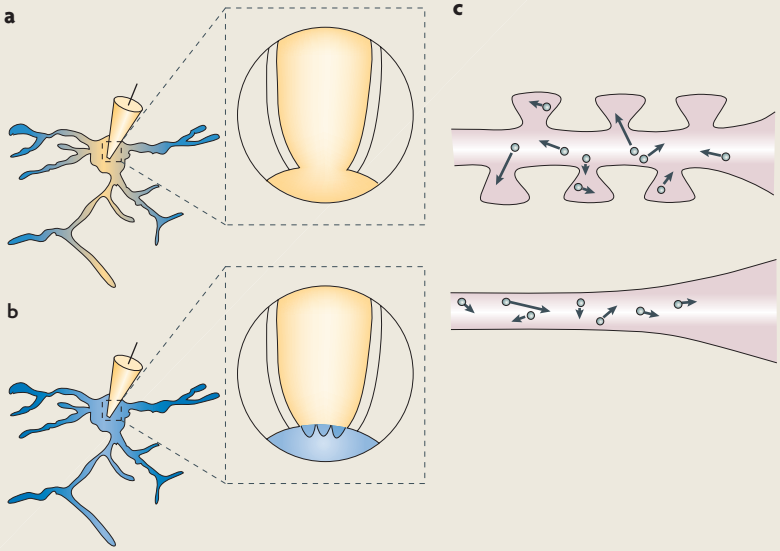
Differential glutamate-receptor expression

Ionotropic receptors. Interneurons also differ from pyramidal neurons (and among one another) in their expression of glutamate-receptor subtypes. Ionotropic glutamate receptors mediate excitatory postsynaptic currents (EPSCs); one type, α-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid receptors (AMPA receptors), underlie fast (millisecond-scale) transmission and are thought to be heterotetramers that consist of different combinations of GluR1–4 subunits (also known as GluRA–D). Most interneurons have much faster synaptic currents than pyramidal neurons[11], a phenomenon that is explained in large part by the fact that they express different subunits[12–16]. In particular, hippocampal interneurons express the GluR4 (or GluRD) subunit to a greater extent than pyramidal cells (in pyramidal cells, the GluR4 subunit is generally only present at very early stages of development)[17]. The GluR2 (or GluRB) subunit is, conversely, expressed to a lower extent in interneurons. Moreover, the 'flip' splice variants of AMPA receptors (which confer slower deactivation and desensitization kinetics[18]) predominate in pyramidal neurons, whereas the 'flop' splice variants are more abundant in interneurons.

Although interneurons as a whole express GluR2 at a lower level than pyramidal cells, there is further variability in the abundance of this subunit among different inhibitory cells. Post-transcriptional editing of GluR2 results in the presence of an arginine residue in the ion conduction pathway, making the channel impermeable to Ca^{2+}. This Ca^{2+} impermeability is typical of AMPA receptors in pyramidal neurons. Receptors that lack GluR2 or that contain the unedited versions of the subunit are permeable to Ca^{2+}, and are also susceptible to voltage-dependent blockade by polyamines[19] (FIG. 1). These positively charged molecules (especially spermine and spermidine) are normally present in the cytoplasm, and they occlude the pore when the membrane is depolarized[19–21]. The identity of the AMPA receptors that are mediating glutamatergic transmission can therefore be inferred from the voltage dependence of the EPSCs, as long as dilution of polyamines from the cytoplasm is prevented (this is most simply achieved by supplementing the recording pipette solution with spermine). Ca^{2+}-permeable AMPA receptors (CP-AMPARs) characteristically mediate a synaptic conductance that decreases with depolarization, hence their alternative description as rectifying AMPA receptors. Interestingly, synapses on interneurons that contain CP-AMPARs often have a very small NMDA-receptor-mediated component[22–24] (FIG. 1b). Conversely, interneuron synapses that have non-rectifying AMPA receptors (Ca^{2+}-impermeable receptors or CI-AMPARs) are more likely to behave like glutamatergic synapses on pyramidal neurons, with a large NMDA-receptor-mediated component (although exceptions to this rule have been reported[25]) (FIG. 1a).

Box 2 | **Perforated patch recording**

A shortcoming of whole-cell recording (illustrated in panel **a**) is that long-term potentiation often cannot be induced because of cytoplasmic 'washout' of as-yet unidentified constituents. The perforated patch method (panel **b**) obviates this problem by recording with cation-selective membrane pores that are made by an antibiotic (such as gramicidin) that is included in the pipette solution. Panel **c** illustrates how cytoplasmic washout might be faster in interneurons than in pyramidal neurons because the numerous spines of pyramidal neurons effectively retard the diffusion of intracellular molecules along the dendrites[94].



Acute brain slice
An experimental preparation that consists of freshly isolated slabs of brain tissue maintained in a chamber that is supplied with oxygenated artificial cerebrospinal fluid. It allows synaptic and neuronal properties to be studied with electrophysiological, optical, pharmacological and biochemical methods.

Latency jitter
Information transmission in the brain can be degraded in several ways – latency jitter describes trial-to-trial variability in the initiation of a synaptic signal or action potential.

Theta band
The frequency range of the power spectrum of an electroencephalograph that ranges from approximately 4Hz to 8 Hz.

Theta oscillation
A type of brain activity that is characterized by prominent theta-band neuronal and synaptic activity. It typically occurs during exploratory activity in freely moving rodents.

Variability in NMDA-receptor expression in different interneurons has also been noted with immunohistochemical methods[26], although the available data are not easily related to the interneuron types mentioned above. NMDA receptors make an important contribution to spike-timing in interneurons[27], but their role in the synaptic plasticity of this class of cells has received little attention until recently.

In contrast to CP-AMPARs, NMDA receptors are blocked by Mg^{2+} ions at relatively negative membrane potentials (resting membrane potentials), but permit Ca^{2+} flux when the cell is depolarized. This implies that the two extreme types of synapse have diametrically opposite properties with respect to the conditions that are necessary for maximal glutamate-triggered Ca^{2+} influx: postsynaptic hyperpolarization in the case of synapses that are equipped with CP-AMPARs but few NMDA receptors, and postsynaptic depolarization in the case of synapses that are equipped with CI-AMPARs and abundant NMDA receptors (FIG. 1). If depolarization equates to activity, and hyperpolarization to quiescence, then the conditions under which Ca^{2+} enters the postsynaptic cell can be compared to two logical gates: coincident pre- AND postsynaptic activity in the case of synapses that are equipped with NMDA receptors, and coincident pre- AND.NOT postsynaptic activity in the case of synapses that are equipped with CP-AMPARs (FIG. 1c,d). As we discuss below, emerging LTP-induction rules approximate to either one or the other of these logical conditions in distinct pathways in the hippocampal inhibitory circuit.

Immunohistochemical and *in situ* hybridization studies give only an indirect clue as to the biophysical properties of AMPA receptors, because they have limited ability to discriminate between GluR2 and GluR3, or to detect whether any GluR2 subunit that is present is edited. Nevertheless, the available data suggest that CP-AMPARs are especially common in interneurons that are immunopositive for parvalbumin, nitric oxide synthase (NOS) and/or calretinin[28,29]. The functional implications of this correlation remain to be determined. Several of these immunochemically identified cell groups, in particular parvalbumin-positive cells, are implicated in feedback inhibition. However, CP-AMPARs are also present at some of the synapses that are made by hippocampal mossy fibres on interneurons in the stratum lucidum of CA3, which contribute to feedforward inhibition[23]. Interestingly, not all glutamatergic synapses on individual interneurons exhibit the same rectification properties[30]. This observation implies that mechanisms exist to target receptors differentially to distinct synapses, possibly reflecting differences in the identities of the presynaptic principal cells that innervate them.

Metabotropic receptors. Metabotropic glutamate receptors (mGluRs) are also implicated in long-term plasticity in interneurons. The mGluR1 subtype (one of the group I mGluRs) is strongly expressed in O-LM cells, together with CP-AMPARs. Other interneuron types (including fast-spiking parvalbumin-positive cells) do not express mGluR1 abundantly[31,32], implying that the two receptors are not obligate partners. The group III receptor mGluR7 has also been implicated in long-term plasticity at synapses made by hippocampal mossy fibres (discussed further below). However, in this case, the receptor is expressed presynaptically.

LTP and LTD: classification

Navigating the literature on LTP and LTD in hippocampal interneurons is difficult, in large part because inconsistent induction protocols and different recording methods have been applied to their study. In addition, only some studies have addressed whether synaptic plasticity is restricted to the synapses that were stimulated. Rather than listing the outcome of every reported experiment, we have attempted to distil some relatively consistent principles, and have therefore divided reports on the basis of whether or not they found plasticity to require NMDA receptors. Any studies that did not explicitly test the role of NMDA receptors pharmacologically could therefore not be classified (see REFS 33,34).

NMDA-receptor-dependent LTP

Although activity-dependent synaptic plasticity in interneurons has come under intense scrutiny only in recent years, LTP in these cells was first reported 25 years ago[35]. LTP was induced by high-frequency tetanic stimulation *in vivo*, and therefore this original observation bears considerable similarity to the discovery of LTP in principal cells[36]. Subsequent *in vitro* studies have confirmed that tetanic stimulation can elicit LTP of

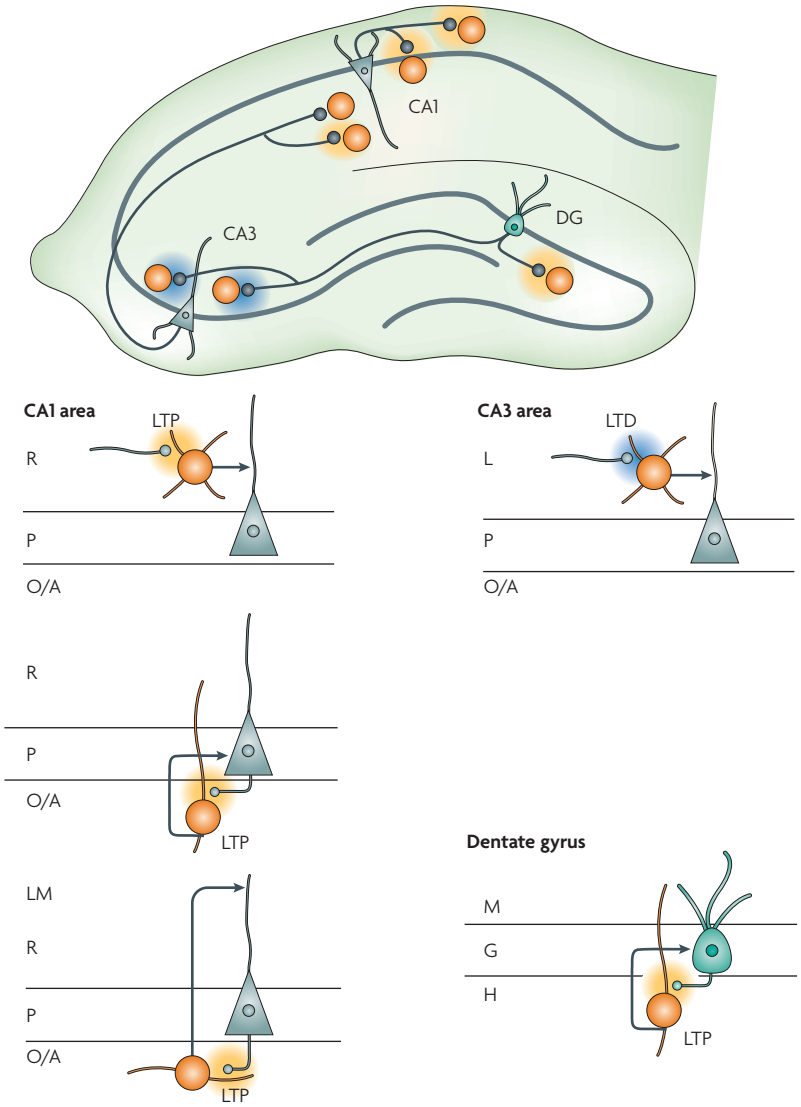


Figure 2 | **Long-term potentiation (LTP) and long-term depression (LTD) in the hippocampal formation.** NMDA-receptor-dependent LTP, also called Hebbian LTP (see BOX 3) occurs in approximately 50% of interneurons in the stratum radiatum of the CA1 region, at synapses formed by Schaffer collaterals[45] (axons of CA3 pyramidal cells). When measured by whole–cell patch-clamp recording, tetanic stimulation of Schaffer collaterals has been shown to induce LTD in interneurons of the stratum radiatum[33]. This form of LTD spreads to other inputs on the same interneuron. Anti-Hebbian LTP, which is dependent on Ca^{2+}-permeable AMPA receptors (CP-AMPARs) and involves mGluR1, occurs in many interneurons in the stratum oriens and the stratum pyramidale, at synapses formed by axon collaterals of local pyramidal neurons[24,57]. Both LTP and LTD occur in basket cells in the dentate gyrus (DG), at synapses formed by axon collaterals of granule cells[34]. LTD that is dependent on either NMDA or CP-AMPARs occurs in interneurons in CA3, where it has been studied most intensively at synapses that are formed by mossy fibres[23,65]. AMPA, α-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid; G, stratum granulosum; H, hilus; L, stratum lucidum; LM, stratum lacunosum-moleculare; M, stratum moleculare; NMDA, *N*-methyl-D-aspartate; O/A, stratum oriens/stratum alveus; P, stratum pyramidale; R, stratum radiatum.

Gamma band
The 30–70 Hz range of the electroencephalograph power spectrum. It is associated with high-level information processing.

glutamatergic responses in some non-pyramidal neurons of the hippocampus[37]. This finding has been extended in another study that compared interneurons in the stratum radiatum with 'giant' glutamatergic neurons, which also occur in this region and also express LTP after tetanic stimulation[38,39].

The NMDA receptor requirement of LTP induction. A potential pitfall of eliciting LTP with tetanic stimulation is that, if the response to a test stimulus is contaminated by a disynaptic EPSC (or excitatory postsynaptic potential; EPSP), then LTP in an interposed glutamatergic neuron can be misinterpreted as LTP occurring at the synapses on the interneuron itself[40]. The main justification for using tetanic stimulation to study LTP is that glutamate release from multiple synapses leads to postsynaptic depolarization, mainly, at first, through AMPA receptors, thereby allowing NMDA-receptor activation. The conditions that are necessary for NMDA-receptor activation can also be achieved by direct depolarization of the postsynaptic neuron using the recording electrode, paired with low-frequency presynaptic stimulation. Using such an induction protocol, both LTP and LTD have been reported in hippocampal interneurons[25,41,42], although two studies reported no long-lasting plasticity[33,43]. In another study on interneurons in the stratum radiatum of the CA3 region in the immature rat, NMDA-receptor-dependent LTP was elicited only when it was paired with moderate depolarization, and only in synapses with CP-AMPARs. Pairing with more intense depolarization in this experimental setup led instead to LTD, suggesting a complex relationship between the outcome of pairing and the degree of Ca^{2+} influx[25].

Most recent studies on interneuron plasticity have relied on whole-cell patch-clamp recordings[25,33,34,37,38,40–43]. A potential pitfall of this method when it is applied to pyramidal neurons is that LTP cannot be elicited reliably if the induction protocol is delayed for more than 20 minutes or so. This is presumably because some necessary ingredient becomes diluted from the cytoplasm, as demonstrated by the finding that LTP can still be elicited after a protracted recording period when using the perforated patch method[44] (BOX 2). Using this approach, NMDA-receptor-dependent LTP was elicited in approximately 50% of interneurons in the stratum radiatum of the CA1 region of the hippocampus, by pairing presynaptic stimulation with postsynaptic depolarization[45]. In the other 50% of interneurons, the same induction protocol had no effect on synaptic strength. Characterization of AMPA and NMDA-receptor-mediated currents after LTP induction confirmed that this potentiation occurred only at synapses that had a large NMDA-receptor-mediated component and, typically, non-rectifying AMPA receptors[24,25]. Repeating the experiments with conventional whole-cell recordings was almost universally unsuccessful using this protocol, confirming that washout of as-yet unidentified constituents that are necessary for LTP induction occurs much faster in interneurons than in pyramidal neurons. Although differences in recording methods potentially provide a simple explanation as to why apparently similar induction protocols have[45] or have not[33] yielded LTP, one study reported no plasticity, even with perforated patch recordings[43]. Additional methodological differences may need to be explored before we can explain this discrepancy.

LTP in aspiny interneurons. Stimulating two populations of axons that converge on the same interneuron (afferent 'pathways') allows one to ask whether

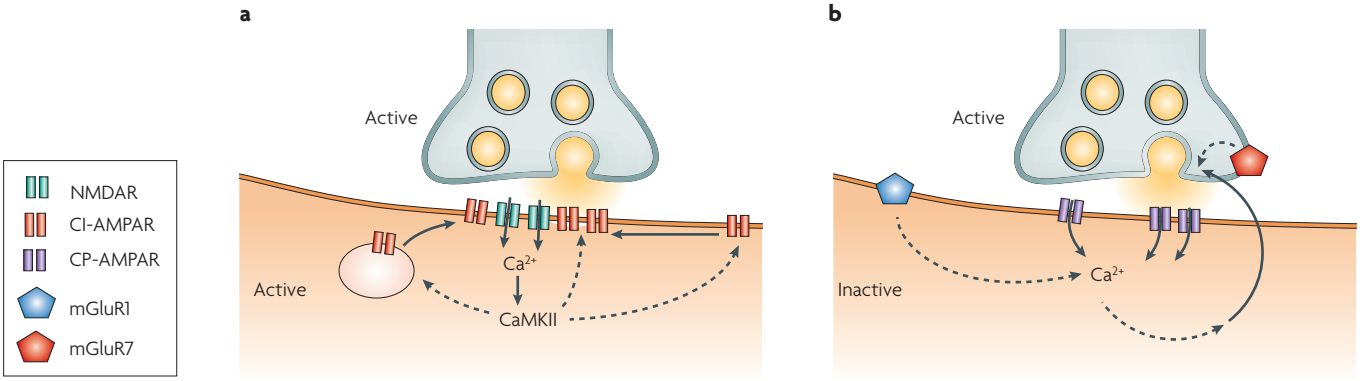


Figure 3 | **Complementary forms of synaptic plasticity at different types of glutamatergic synapse. a** | Long-term potentiation (LTP) at synapses with NMDA receptors and Ca^{2+}-impermeable AMPA receptors (CI-AMPARs) appears to obey broadly the same induction and expression rules as LTP in pyramidal neurons[45]. Coincidence of pre- and postsynaptic activity causes Ca^{2+} influx through NMDA receptors, triggerings a CaMKII-dependent induction cascade. By analogy with LTP in pyramidal neurons, LTP expression is likely to depend largely on the insertion of AMPA receptors into the synaptic plasma membrane and/or a change in their phosphorylation status. Therefore, NMDA-receptor-dependent LTP appears to be expressed postsynaptically[68]. **b** | LTP at synapses with CP-AMPARs also depends on postsynaptic Ca^{2+}, but is accompanied by changes in trial-to-trial variability, failure rate, paired-pulse ratio and AMPA receptor occupancy that point to a presynaptic locus of expression[24,68]. The identity of the retrograde factor remains to be determined. Both forms of LTP have their corresponding counterparts in two complementary forms of LTD. Metabotropic glutamate receptors have metaplastic roles in NMDA-receptor-independent plasticity at some synapses: postsynaptic mGluR1 has a role at synapses made by local pyramidal cell axon collaterals on putative O-LM cells[57]; presynaptic mGluR7 has a role at synapses formed by mossy fibres[71]. These receptors also detect glutamate release and trigger incompletely understood G-protein-dependent signalling cascades that modulate synaptic plasticity. AMPA, α-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid; NMDA, *N*-methyl-D-aspartate.

LTP is restricted to synapses that were active during postsynaptic depolarisation. Remarkably, NMDA-receptor-dependent LTP in interneurons was restricted to the afferent pathway whose stimulation was paired with depolarization[45]. Another pathway that was not stimulated during the induction protocol remained unaffected (in contrast to a study of LTP in amygdalar interneurons[46]). Although this pathway specificity recapitulates what is known about LTP in pyramidal cells, it is unexpected in cells that lack abundant dendritic spines. Spines are generally assumed to compartmentalize biochemical processes, including those that underlie synaptic plasticity[47,48]. Indeed, the finding of pathway-specific LTP in aspiny cells calls into question the widely held assumption that local confinement of changes in synaptic strength is the main adaptive role of spines. If spines do not underlie the pathway specificity of LTP in interneurons, then what does? One possible answer is that synaptically evoked Ca^{2+} transients can be confined to micrometre-scale fragments of aspiny dendrites[49]. It will be important to determine whether the restriction of intersynaptic diffusion of Ca^{2+} ions by interaction with endogenous Ca^{2+}-buffering proteins can fully account for the pathway specificity of LTP. It should, of course, be borne in mind that the pathway specificity of LTP is not strictly equivalent to synapse specificity, because limited intersynaptic spread of Ca^{2+} (or of elements of the Ca^{2+}-dependent signalling cascade that is involved in LTP induction) along the dendrite would not necessarily be detected in experiments in which synaptic signals are generated relatively sparsely through the dendritic arborization.

In pyramidal neurons, a necessary step in the LTP-induction cascade downstream of Ca^{2+} influx through NMDA receptors is activation of Ca^{2+}–calmodulin-dependent kinase II-α (αCaMKII)[50]. This kinase is unusual in that it can remain in an activated state following removal of the initial Ca^{2+} stimulus, through autophosphorylation at a threonine residue (T286 in mice). An essential role for autophosphorylation is demonstrated by the absence of pyramidal cell LTP in mice that harbour a point mutation in αCaMKII that changes threonine 286 to alanine (T268A)[51]. However, αCaMKII is conspicuously absent from interneurons[52,53]. Although NMDA-receptor-dependent LTP in hippocampal interneurons is abolished by pharmacological blockade of Ca^{2+}–calmodulin-dependent kinases, it remains operative in αCaMKII T286A mutant mice[54]. One possible explanation is that in interneurons another related kinase, for example, βCaMKII, carries out the role that αCaMKII has in pyramidal neurons. Some degree of redundancy between these isoenzymes is supported by the finding that introduction of the activated form of αCaMKII into hippocampal interneurons leads to a strong potentiation of synaptic strength[42], much as it does in pyramidal neurons[55].

LTP occurs in the feedforward inhibitory pathway. In the CA1 area of the hippocampus, NMDA-receptor-dependent LTP could be elicited in only approximately 50% of interneurons in the stratum radiatum, and it was very rare in interneurons in the stratum pyramidale and the stratum oriens[24,45] (FIG. 2). Many interneurons in the stratum radiatum are involved in feedforward

Sharp-wave ripple
A brief (approximately 100 ms) episode of high-frequency (> 100 Hz) population activity.

AMPA receptor
An ionotropic glutamate receptor that is characterized by fast kinetics. Its name is derived from the potent and specific agonist α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid. AMPA receptors can be differentiated into Ca^{2+}-permeable and Ca^{2+}-impermeable subtypes.

Post-transcriptional editing
The processing that some mRNA transcripts (including those that encode some of the AMPA and kainate receptor subunits) undergo before splicing and translation. One form of post-transcriptional editing results in the substitution of an arginine (R) codon for a glutamine (Q) codon: a change that affects several biophysical properties.

Rectifying AMPA receptor
An AMPA receptor that has a conductance that decreases with depolarization, and thus deviates from Ohm's law.

Non-rectifying AMPA receptor
An AMPA receptor that contains an edited GluR2 subunit and has a voltage-independent conductance.

Mossy fibres
The axons of dentate granule cells. They project to the hilus of the dentate gyrus and to the CA3 region of the hippocampus proper. These axons have several unusual properties, including abundant presynaptic expression of the metabotropic glutamate receptor mGluR7, and the occurrence of giant boutons that synapse on CA3 pyramidal neurons. Mossy fibres also synapse with interneurons in the hippocampus.

Metabotropic glutamate receptors
A family of eight G-protein-coupled glutamate receptors that have a characteristic seven-transmembrane segment topology. They are grouped into three classes (I–III) depending on their pharmacological properties and their downstream metabolic cascades.

Tetanic stimulation
The high-frequency activation of axons evokes a postsynaptic signal in which the responses to individual presynaptic action potentials merge together (a tetanus) – such stimulation is said to be tetanic.

inhibition of local principal cells, and at least some of the cells that exhibit LTP have been shown to innervate CA1 pyramidal cells monosynaptically[45]. Moreover, LTP in the feedforward system has been shown to lead to a potentiation of disynaptic inhibition of principal cells. To date, little is known about the expression mechanisms of NMDA-receptor-dependent LTP in interneurons. However, the observation that LTP does not affect short-term plasticity (as measured by delivering paired-pulse stimulation) argues against a presynaptic change in release probability[45].

Morphological and neurochemical properties that correlate with the ability to induce LTP remain to be identified. Especially intriguing are the identity and abundance of Ca^{2+}-buffering proteins, which, as mentioned above, are likely to have a major role in constraining the spatiotemporal profile of Ca^{2+} transients following NMDA receptor activation in interneurons.

NMDA-receptor-independent LTP

The role of CP-AMPARs and mGluRs. Although pharmacological blockade of NMDA receptors generally prevents LTP induction in most pyramidal neurons, high-frequency (100 Hz) tetanic stimulation can induce LTP independently of these receptors at some synapses, most notably those formed by mossy fibres on CA3 pyramidal neurons. Prolonged high-frequency activity in multiple axons does not occur naturally in the brain, so the physiological relevance of tetanic stimulation-induced LTP is uncertain. Lower-frequency stimulation, or brief bursts of high-frequency stimulation repetitively delivered to presynaptic axons, more closely resemble activity in the intact brain. Such patterns have been shown to result in NMDA-receptor-independent LTP in interneurons of the amygdala[56] and of the stratum oriens of the hippocampus[24,57]. These forms of LTP require an elevation of postsynaptic Ca^{2+} for their induction (FIG. 3). In this respect, they are strikingly different to the LTP that occurs in the mossy fibres of CA3 pyramidal neurons, which has been shown to withstand chelation of postsynaptic Ca^{2+} (REFS 58,59, however, see REFS 60,61).

There are two main candidate mechanisms for NMDA-receptor-independent postsynaptic Ca^{2+} elevation: one that involves CP-AMPARs (see below) and one that involves mGluR activation. mGluR1 activation is necessary for LTP induction in at least some interneurons of the stratum oriens, where LTP is blocked by the selective antagonist LY367,385 (REF. 57). Indeed, O-LM cells express this subunit abundantly[31,32]. This observation is consistent with a permissive role for mGluR1, and it does not prove that mGluR1 activation is sufficient to induce LTP. Synaptically induced postsynaptic Ca^{2+} transients in these neurons depend on both mGluRs and CP-AMPARs[62]. Given the rectification properties of CP-AMPARs, Ca^{2+} influx through such receptors might be expected to occur only when the postsynaptic membrane potential is relatively negative (when it is at rest, close to rest or hyperpolarized).

CP-AMPAR-dependent LTP. When recording with perforated patches, or with polyamines that had been added to the whole-cell recording pipette solution, LTP was recently found to be readily elicited at synapses made by local axon collaterals on approximately 75% of interneurons in the stratum oriens of the CA1 region (although it was blocked by postsynaptic depolarization)[24]. LTP could also be induced by stimulating presynaptic axons at low frequency, as long as the postsynaptic membrane was sufficiently hyperpolarized. Brief high-frequency stimulus bursts also led to LTP, but only when the stimuli themselves failed to depolarize the membrane by more than a few millivolts from rest. An obligatory requirement for AMPA receptors was demonstrated by showing that blocking these receptors during the induction protocol failed to elicit LTP. Not surprisingly, the AMPA receptors that mediated the EPSCs were found to be strongly rectifying (implying Ca^{2+} permeability) in all cases in which NMDA-receptor-independent LTP was induced[24].

NMDA-receptor-independent LTP in interneurons in the stratum oriens has also been reported to be induced by mGluR1 activation[57]. Are these two forms of LTP (CP-AMPAR-dependent[24] and mGluR1-dependent[57]) one and the same? Arguing against such a unified model, LTP that is dependent on mGluR1 was shown to require postsynaptic depolarization coupled with presynaptic high-frequency burst stimulation — it was not elicited when the same presynaptic stimulation was delivered to a hyperpolarized postsynaptic neuron[57,63]. However, in these experiments, polyamines were not added to the pipette solution, so the normal depolarization-dependent blockade of rectifying CP-AMPARs might have been compromised (FIG. 1b). Moreover, failure to induce LTP might have occurred because of the whole-cell washout phenomenon (see also REF. 43). The answer is not known for certain, but for the purpose of this Review, we tentatively suggest that these are indeed two sides of the same coin.

Although NMDA-receptor-independent LTP is most evident in O-LM cells[24,57,63], it has also been elicited in several other interneurons (including axo-axonic cells and one type of basket cell[24]), at synapses that were activated by stimulating the axon collaterals of local principal cells. By contrast, it is rare at Schaffer collateral synapses on interneurons in the stratum radiatum[24]. The interneurons that have been identified as showing NMDA-receptor-

Box 3 | **Hebbian and anti-Hebbian synaptic plasticity**

The use of the term 'Hebbian' to describe long-term potentiation (LTP) that is dependent on *N*-methyl-D-aspartate (NMDA) receptors has gained widespread acceptance because it approximates Hebb's postulate, which effectively states that strengthening of excitatory transmission should follow the conjunction of pre- and postsynaptic activity[73,74]. The term 'anti-Hebbian' is more problematic. It has been used by many to describe long-term depression (LTD) that develops after a Hebbian coincidence of presynaptic action potentials and postsynaptic depolarization ('anti-Hebbian LTD' — see for instance REFS 95,96). This nomenclature places the emphasis on the outcome of the pairing event, although the term is arguably a tautology. The surprising finding that presynaptic firing, when it coincides with a negation of postsynaptic activity (the postsynaptic membrane potential remains close to or negative to its resting value), can lead to LTP at some synapses that express Ca^{2+}-permeable α-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid (AMPA) receptors arguably has a stronger claim to 'anti-Hebbian', hence the term 'anti-Hebbian LTP'[24].

independent LTP are involved in feedback inhibition. However, several of these cells also receive excitatory inputs from more remote structures and/or project to interneurons[3]. It therefore remains to be determined whether NMDA-receptor-independent LTP is restricted to the first (glutamatergic) synapse in the feedback inhibitory circuit, or whether it is instead a more general property of these interneurons. Interneurons that are immunopositive for parvalbumin, NOS, calretinin and calbindin in general express low levels of the GluR2 subunit[29], and are therefore potential candidates for exhibiting NMDA-receptor-independent LTP.

Although the above results provide compelling evidence that Ca^{2+} influx through CP-AMPARs triggers NMDA-receptor-independent LTP, they also hint at an important role for mGluR1. Indeed, mGluR1 is expressed abundantly in O-LM cells, although it is less abundant in other interneurons[31,32] that also exhibit NMDA-receptor-independent LTP[24]. One possible role of mGluRs is to lower the threshold for LTP induction, to allow, for instance, tetanic-stimulation-induced LTP to occur during moderate postsynaptic depolarization[24]. Such a role is consistent with Ca^{2+} imaging data, which show that the activation of metabotropic glutamate receptors evokes Ca^{2+} transients in the dendrites of interneurons in the stratum oriens, with both transient receptor potential channels and intracellular Ca^{2+} stores being involved[62].

LTP that is dependent on CP-AMPARs in interneurons has been shown to be pathway specific[24], just as was demonstrated for NMDA-receptor-dependent LTP[45]. This is again consistent with evidence that Ca^{2+} transients that are mediated by synaptic activation of CP-AMPARs can be confined to fragments of aspiny dendrites[64]. However, in contrast to NMDA-receptor-dependent LTP, NMDA-receptor-independent LTP in interneurons of the stratum oriens is accompanied by changes in the paired-pulse ratio, failure rate and coefficient of variation of EPSCs, all of which argue for an increase in presynaptic release probability[24,57]. A similar pattern was reported in association with LTP at synapses made by mossy fibres on dentate gyrus basket cells, although NMDA-receptor-independence was not tested explicitly[34]. An alternative insight into whether LTP is expressed pre- or postsynaptically can be obtained from the sensitivity of the EPSP to extracellularly applied polyamines, because these act as use-dependent blockers of CP-AMPARs. The greater the cumulative occupancy of receptors by glutamate that has been released from presynaptic axons, the greater the reduction in EPSP amplitude. In keeping with a presynaptic site of expression, extracellular polyamines were found to have a greater effect on EPSPs after induction of NMDA-receptor-independent LTP than in a control pathway[24]. The steps that lead from a rise in Ca^{2+} concentration in the postsynaptic neuron to a presynaptic increase in transmitter release remain to be elucidated (FIG. 3b).

Long-term depression in interneurons

LTD of glutamatergic signalling has been demonstrated at synapses on several interneurons in the hippocampal formation[33,34,65], and it has been studied especially intensively at synapses made by hippocampal mossy fibres in the stratum lucidum of the CA3 region[23,66] (FIG. 2). Interneurons in this area are innervated by mossy fibres through synapses that are equipped with either CP-AMPARs or CI-AMPARs. Although LTD can be elicited by high-frequency stimulation at both types of synapse, it is dependent on postsynaptic Ca^{2+} influx through NMDA receptors at only those synapses that express CI-AMPARs[23]. At synapses that express CP-AMPARs, LTD also requires a postsynaptic Ca^{2+} elevation[65,67]. However, as was mentioned above, the dichotomy of synapse types may not always be so absolute, and relatively small changes in membrane potential appear to result in different outcomes of pairing protocols[25].

The induction and expression mechanisms of the various forms of LTD are strikingly different (FIG. 3). The disruption of postsynaptic AMPA-receptor trafficking prevents NMDA-receptor-dependent LTD in interneurons, consistent with LTD that is expressed by endocytosis of AMPA receptors[68], and similar to what has been reported for pyramidal neurons[69,70]. By contrast, NMDA-receptor-independent LTD has a joint requirement for both postsynaptic Ca^{2+} signalling and presynaptic activation of mGluR7, and also involves protein kinase C[65,67,68,71]. NMDA-receptor-independent LTD appears to occur presynaptically, because it is accompanied by an increase in the paired-pulse ratio and a decrease in AMPA-receptor occupancy[68]. At mossy fibre synapses, it is accompanied by a persistent decrease in the contribution of P/Q-type Ca^{2+} channels to presynaptic action-potential-dependent Ca^{2+} transients[67].

NMDA-receptor-independent LTD does not appear to be accompanied by a change in the type of AMPA receptors that are expressed at the synapse, in contrast to cerebellar stellate cells, in which high-frequency activation of CP-AMPARs has been shown to lead to a switch in glutamate-receptor subtypes[72]. Surprisingly, recent evidence suggests that the same pattern of activity that leads to LTD at mossy fibre synapses can cause internalization of presynaptic mGluR7, switching the synapse into a state in which subsequent tetanic stimulation leads to potentiation[71]. This implies that mGluR7 receptors can act as a metaplastic switch, the state of which influences the outcome of high-frequency activity in the glutamatergic synapses. Apart from this study, relatively little is known about the ability of synapses on the same interneuron to exhibit bi-directional plasticity[34,25].

Again, several steps in the induction and expression cascades remain to be identified — not least the identity of the retrograde messenger that signals the postsynaptic Ca^{2+} transient to the presynaptic structure. A note of caution that must be applied to any interpretion of the available evidence is that many of these studies were carried out with whole-cell recording: it will be important to determine whether the same plasticity phenomena occur in interneurons under conditions in which the cellular processes that contribute to synaptic plasticity remain intact. Indeed, an early study of tetanic-stimulation-induced plasticity in interneurons of the stratum radiatum reported no change in synaptic strength when

Whole-cell patch-clamp recording
A variation of the patch-clamp method whereby the membrane under the mouth of a pipette that has been applied to a neuron is ruptured, providing excellent electrical access to the neuron. The drawback of this technique is that cytoplasmic integrity is compromised.

Protracted recording period
When a whole-cell patch-clamp recording lasts longer than approximately 20 minutes, precluding LTP induction in pyramidal cells. In aspiny interneurons, the viable recording period before LTP induction is much shorter.

Perforated patch method
A variant of the cell-attached patch-clamp method in which the membrane under the mouth of the pipette is not ruptured, but instead an antibiotic (typically gramicidin, nystatin or amphotericin B) is included in the pipette solution to form ion-conducting pores. This allows good electrical access to the cell without compromising cytoplasmic integrity.

Aspiny dendrites
Dendrites that are devoid of spines or equipped with only sparse spines. Cortical inhibitory interneurons typically have aspiny dendrites.

Transient receptor potential channels
A family of ion channels that are related to voltage-gated potassium channels. Many are permeable to multiple cations and are opened in response to intracellular messengers.

Paired-pulse ratio
A measure of short-term, use-dependent synaptic plasticity that is obtained by dividing the response to the second of two stimuli by the response to the first stimulus. A presynaptic alteration in release probability is almost universally accompanied by a change in paired-pulse ratio.

Failure rate
The rate at which a synapse fails to release any neurotransmitter and hence to generate any postsynaptic response (action-potential-dependent neurotransmitter release is probabilistic). The failure rate gives an indirect indication of the state of the presynaptic release machinery.

Coefficient of variation of EPSCs
The standard deviation of action-potential-dependent EPSCs divided by their mean amplitude. This measure is used to describe the EPSCs' trial-to-trial amplitude fluctuation. An increase in transmitter release probability is typically associated with a decrease in the coefficient of variation.

Hebbian LTP
A type of long-term potentiation in which the induction rules approximate Hebb's postulate (the need for a conjunction of pre- and postsynaptic activity).

Asynchronous afferent volley
When multiple input axons fire independently of one another.

low-frequency presynaptic stimulation was paired with depolarization. However tetanic stimulation led to LTD, which spread to a control pathway[33]. These results are incongruent with the NMDA-receptor-dependent LTP that is observed in 50% of interneurons in the same region of the hippocampus when they are studied with perforated patch recordings[24,45].

The computational roles of LTP and LTD

The joint requirement of NMDA receptors for presynaptic glutamate release and postsynaptic depolarization is broadly in line with the cellular learning rule that was proposed by D. Hebb in the mid-twentieth century[73,74]. NMDA-receptor-dependent LTP is therefore frequently termed 'Hebbian LTP'. Theoretical analyses of networks of simplified neurons that are connected by Hebbian synapses have provided a fertile ground for insights into the possible mechanisms of memory storage and recall to flourish. By analogy, in this Review, we use the term 'anti-Hebbian LTP' to describe LTP that is dependent on rectifying CP-AMPARs and that is induced by repetitive presynaptic glutamate release under conditions in which the postsynaptic membrane is relatively hyperpolarized. This is distinct from 'anti-Hebbian LTD', which, perhaps confusingly (BOX 3), has been used to describe a weakening of synaptic strength that is triggered by the conjunction of pre- and postsynaptic activity. This description fits both NMDA-receptor-dependent LTD and NMDA-receptor-independent LTD, as both require postsynaptic Ca^{2+}-dependent signalling together with presynaptic glutamate release. What might be the adaptive roles of these three forms of synaptic plasticity?

Hebbian LTP in interneurons. Hebbian (or NMDA-receptor-dependent) LTP appears to occur predominantly in the feedforward inhibitory pathway[45]. We can only speculate on the precise conditions under which this form of plasticity might occur in the intact brain, however, if it occurs in parallel with Hebbian LTP in pyramidal neurons, then at least two possible roles can be proposed. First, it may provide a mechanism for rapidly counteracting the net increase in the excitatory drive of pyramidal neurons that accompanies LTP at synapses on principal cells. The Schaffer collateral innervation of CA1 pyramidal neurons is reminiscent of a hetero-associative network that can store multiple memory traces[75]. Assuming that associations between patterns of input and output activity are established by strengthening a subset of excitatory synapses in the matrix, then simultaneous strengthening of disynaptic inhibition may act to optimize the information-storage capacity of the network by preventing excessive excitation of the output neurons. Second, because interneurons tend to innervate a high proportion of potential target cells within their axonal arborization (unlike Schaffer collaterals), then LTP in the feedforward circuit may provide a 'centre-surround' inhibition that sharpens memory traces (FIG. 4a).

An alternative insight into Hebbian LTP of feedforward inhibition derives from the ability of the network to perform precise temporal discrimination among asynchronous afferent volleys[6]. If the occurrence of LTP during memory acquisition was restricted to the monosynaptic excitatory inputs to principal cells, then the ability of disynaptic inhibition to maintain a narrow coincidence window for neuronal integration would be compromised. This hypothesis was tested experimentally by comparing the effects of two LTP induction protocols on the ability of individual CA1 pyramidal cells to detect small differences in the timing of action potentials that were elicited in two converging afferent pathways. When LTP was restricted to Schaffer collateral synapses on the recorded pyramidal neuron (by a low-frequency pairing protocol), the ratio of monosynaptic EPSPs to disynaptic inhibitory postsynaptic potentials (IPSPs) was increased and the temporal fidelity of action potential integration was degraded. When, instead, LTP was induced in both the recorded pyramidal neuron and the interposed interneurons that mediate feedforward inhibition, the EPSP/IPSP ratio remained constant and a narrow window of action potential integration was maintained[45] (FIG. 4b).

Anti-Hebbian LTP in interneurons. Before we consider the possible adaptive significance of anti-Hebbian LTP that is dependent on CP-AMPARs, we must ask whether this type of LTP is likely to occur in the intact brain. This depends on whether the membrane potential of neurons remains sufficiently negative during presynaptic activity to permit enough Ca^{2+} flow through CP-AMPARs to trigger LTP induction, or whether it becomes sufficiently depolarized by postsynaptic activity to allow polyamines to block CP-AMPARs efficiently. It has been reported that the polyamine-dependent blockade of CP-AMPARs is rapidly relieved by trains of presynaptic action potentials[76]. However, this result was obtained by including a relatively low concentration of polyamines in the whole-cell pipette solution, and it is possible that, with higher concentrations, the activity-dependent relief of CP-AMPAR blockade occurs to a lesser extent. Some estimates of the effective concentration of cytoplasmic polyamines are consistent with this possibility[19,20], although there is also evidence that the concentration changes during development[77] and in disease[78].

Evidence that distinct activity patterns can gate LTP induction in an anti-Hebbian manner came from a classical associative pairing experiment that used the perforated patch method to record from interneurons in the stratum oriens: when a 'weak' pathway that consisted of burst stimulation of a small number of pyramidal cell axon collaterals was paired with a 'strong' stimulation that was simultaneously delivered to another pathway (which was designed to recruit a larger number of axon collaterals), LTP was not elicited[24]. However, when two weak pathways were stimulated together, or even individually, LTP was elicited, as long as the postsynaptic membrane was not depolarized beyond a few millivolts from rest. The opposite result is obtained in pyramidal cells, in which associative pairing of weak and strong pathways leads to Hebbian LTP (reviewed in REF. 79). These findings suggest strongly that anti-Hebbian LTP can indeed be elicited without any extraneous manipulations of the interneuron membrane potential.

A striking feature of anti-Hebbian LTP is that, in the CA1 region at least, it can be elicited in the feedback rather than the feedforward inhibitory circuit. It may be necessary to look more closely at the conditions under which the induction requirements (the activity of local pyramidal neurons with postsynaptic hyperpolarization) are likely to be met *in vivo*. Although we have little information about membrane potentials in different brain states, the firing patterns of pyramidal neurons and several identified types of interneuron have been documented[3,10,80]. Remarkably, O-LM cells are silenced during sharp-wave ripples, episodes

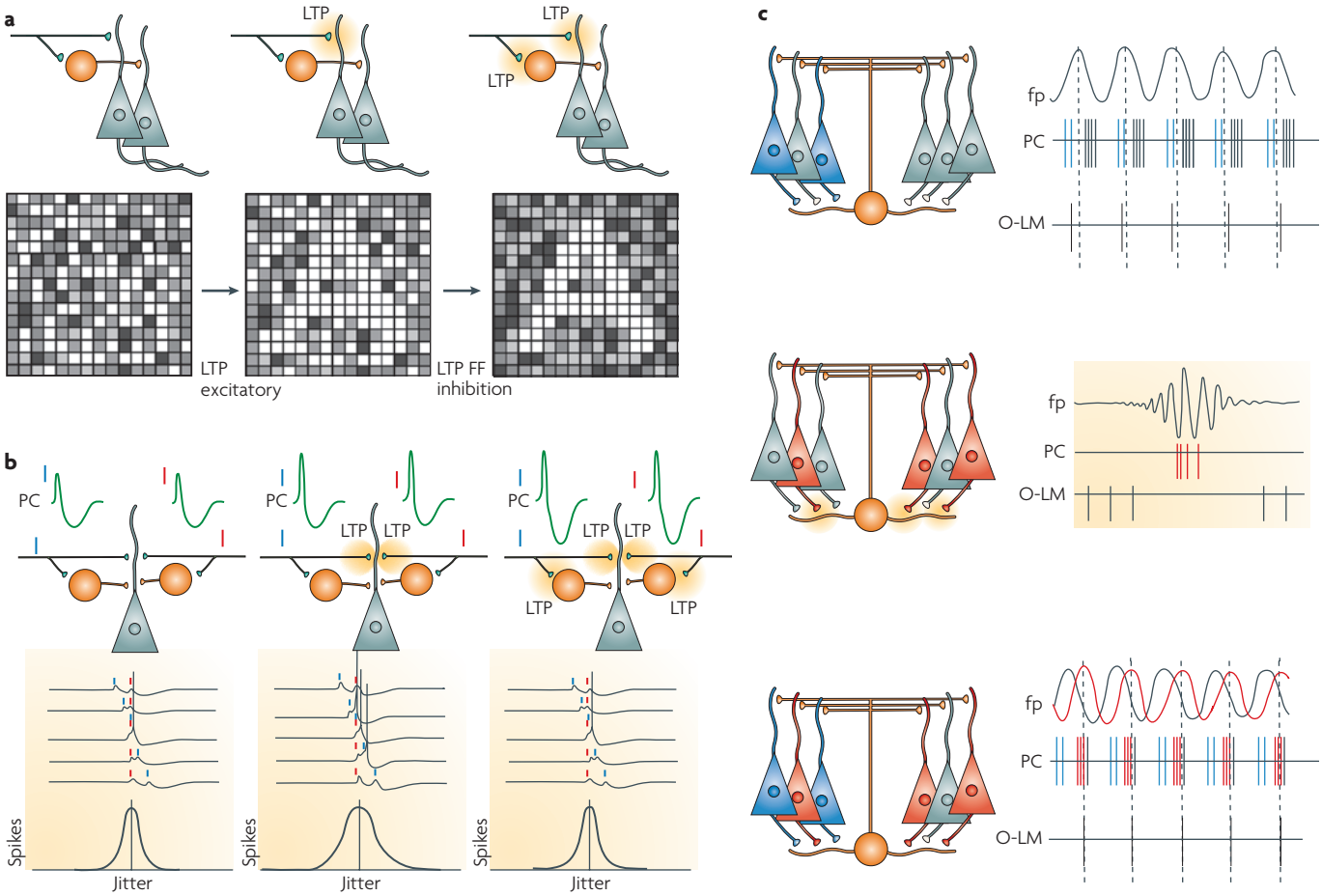


Figure 4 | **The possible computational roles of long-term potentiation (LTP) in cortical interneurons. a** | Hebbian (or NMDA-receptor-dependent) LTP in the feedforward circuit may help to 'sharpen' memory traces by potentiating the disynaptic inhibition of some pyramidal cells. This hypothesis is illustrated schematically by a pattern that is stored exclusively by potentiating the excitation of a subset of principal cells through classical LTP at a subset of sparse excitatory projections (the white tiles in the middle panel). The saliency of the pattern (which is analogous to the 'sharpness' of the memory trace) is enhanced by simultaneously potentiating the feedforward inhibition of the surrounding cells (the dark tiles in the right hand panel). **b |** Hebbian LTP in the feedforward circuit preserves the temporal fidelity of action potential integration by enhancing disynaptic inhibition. Asynchronous afferent volleys become relatively more likely to evoke postsynaptic action potentials in principal cells if the EPSP/IPSP (excitatory/inhibitory postsynaptic potential) ratio increases following LTP at synapses on pyramidal cells (shown in the middle panel). LTP at synapses on feedforward interneurons restores the EPSP/IPSP ratio, allowing precise temporal discrimination[45]. The green traces show EPSP-IPSP sequences that were evoked in pyramidal cells by monosynaptic excitation and disynaptic inhibition. The vertical red and blue lines indicate afferent volleys in two converging pathways: high temporal fidelity of action potential integration is indicated by a narrow spike jitter distribution (bottom). **c** | Anti-Hebbian LTP that occurs during sharp-wave ripples may redistribute the excitatory drive among multiple pyramidal neurons that converge on an O-LM cell. The top panel shows an O-LM cell helping to shape the theta rhythm (4–8 Hz activity) in the population of pyramidal cells, detected as a field potential oscillation[7]. In this schematic, a subset of pyramidal cells (shown in blue) contribute disproportionately to depolarize an O-LM cell. The middle panel shows how, during a sharp-wave ripple, another subset of pyramidal neurons (shown in red) fire at high frequency while the O-LM cell is silenced, approximating the condition for LTP induction. The bottom panel shows how, following the ripple-associated plasticity, the relative importance of different pyramidal neurons in recruiting the O-LM cell is altered, thus affecting the shape of the theta oscillation. The neurons shown in red become more important as sources of depolarization for the O-LM cell, resulting in a change in phase of the theta rhythm. fp, field potential; NMDA, *N*-methyl-D-aspartate; PC, pyramidal cell.

Place cells
Neurons that tend to fire when an animal is in a specific region of its spatial arena. Such behaviour is typical of hippocampal principal cells.

during which pyramidal neurons fire intensely. If O-LM cells are silenced by hyperpolarization (resulting for instance, from GABA release from vasoactive intestinal polypeptide-immunoreactive interneurons[81]), then these are precisely the conditions that are required to induce anti-Hebbian LTP. O-LM cells contribute to theta oscillations (which occur during exploratory behaviour[82]), through phasic inhibition of the apical dendrites of pyramidal neurons[7]. Sharp-wave ripples, on the other hand, occur during slow-wave sleep and consummatory behaviour, and have been circumstantially linked to spatial memory consolidation[83–86]. A post-ripple redistribution of the relative contributions of individual presynaptic cells to O-LM excitation could thus affect the phase and/or frequency of the theta oscillation (FIG. 4c), and could also affect the strength with which different populations of afferent inputs to the circuit (acting through the recruitment of pyramidal neurons and feedforward interneurons, themselves modulated at theta-band frequencies) influence the population behaviour of the circuit. Given that information that is carried by place cells may be partly phase-encoded relative to the theta oscillation[87], such an influence on the oscillation could have extensive repercussions. This phenomenon may even provide a clue to the intriguing finding that the formation of associations between the firing of individual neurons and their spatial loci (that is, the formation of place cells themselves) does not depend on NMDA receptors, unlike the long-term stability of these associations[88]. This implies that another form of long-term plasticity is required to explain the early stages of place cell formation, for which anti-Hebbian LTP in feedback interneurons is a strong candidate.

An alternative and perhaps more prosaic role for anti-Hebbian LTP in the feedback circuit is in 'democratizing' the relative strength of synapses that are supplied by different pyramidal neurons that all converge on a given interneuron. For pyramidal neurons that are already effective in depolarizing their target, LTP at the synapses they supply is likely to be precluded by polyamine blockade of the CP-AMPARs. However, LTP may instead occur at a weak input, such as is supplied by an 'oddball' pyramidal neuron firing out of phase with the majority of principal cells, because glutamate release occurs at a time when the postsynaptic membrane potential is relatively negative. If this phenomenon occurred in O-LM cells, it could have an additional consequence for the theta oscillation of the entire network: as a particular pyramidal neuron became more powerful in recruiting the feedback interneurons, it could increase its contribution to determining the phase of the theta cycle. This could also cause other pyramidal neurons to become entrained to fire together, at which point the condition for anti-Hebbian induction would no longer be met (FIG. 4c).

LTD in interneurons. What about LTD in interneurons (that is, the synaptic weakening that follows the conjunction of pre- and postsynaptic activity)? Although this has been studied most intensely in interneurons in the CA3 region[25,65], in particular at mossy fibre synapses[23,68,71], the extent to which it occurs elsewhere remains to be determined. Moreover, it will be important to determine whether different induction requirements emerge with less invasive recording methods. If LTD in interneurons occurs concurrently with LTP at mossy fibre synapses onto pyramidal neurons, it may act to strengthen the net excitatory drive to the postsynaptic targets in a relatively diffuse manner. Indeed, interneurons far outnumber CA3 pyramidal neurons as postsynaptic targets of mossy fibres[89], and given that LTP at mossy fibre synapses on pyramidal cells is at least partially independent of postsynaptic signalling[59,90], then plasticity in this system might obey very different rules than those obeyed by plasticity in the CA1 region. The metaplastic roles of metabotropic receptors in these forms of plasticity cause further complexity, the possible computational consequences of which are beyond the scope of this Review.

Conclusion

Some of the principles that have been uncovered by studying activity-dependent plasticity in interneurons have extensive neurobiological ramifications. Foremost among these is that the unusual rectification of CP-AMPARs is exploited by the brain to perform a novel logical computation, namely the detection of pre- AND.NOT postsynaptic activity as a necessary condition for LTP at a subset of synapses. Another striking finding is the contrast between the expression mechanisms of plasticity at synapses that are equipped with either CP-AMPARs or CI-AMPARs. Indeed, the degree to which these forms of plasticity are segregated in different pathways in the hippocampus is of immense importance for understanding the conditions under which the traffic of information through interneurons can be modified, both to maintain the normal function of this structure and possibly to encode novel information. Research in this field is clearly in its infancy when compared with the progress that has been made over the past 35 years in LTP research in principal cells. Moreover, we have not considered long-term plasticity at GABA-releasing synapses, which has hitherto received relatively little attention.

A few salient questions can be proposed to guide future work: are distinct types of synapse sensitive to the relative timing of pre- and postsynaptic action potentials, analogous to the spike-timing-dependent plasticity of pyramidal neurons[73]? What are the retrograde messengers that signal the arrival of postsynaptic Ca^{2+} transients (whether they are mediated by CP-AMPARs or by Ca^{2+} release that is triggered by mGluRs) to the presynaptic terminals? When interneuron classification eventually matures, will it be possible to predict with certainty which particular form of plasticity is exhibited by each synapse (if synapses are defined by presynaptic axon identity and postsynaptic interneuron type)? Perhaps the most challenging question that remains to be answered is how the immense potential computational power that is represented by these forms of plasticity contributes to organizing the temporal structure of cortical rhythms, and in storing information. Experimental and theoretical efforts to address these questions will no doubt be rewarded by exciting discoveries.

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Competing interests statement
The authors declare no competing financial interests.

DATABASES

Entrez Gene: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
αCaMKII | βCaMKII | calbindin | calretinin | CCK | GluR2 | GluR3 | GluR4 | mGluR1 | mGluR7 | parvalbumin |

FURTHER INFORMATION

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