Metaplasticity: tuning synapses and networks for plasticity

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Abstract | Synaptic plasticity is a key component of the learning machinery in the brain. It is vital that such plasticity be tightly regulated so that it occurs to the proper extent at the proper time. Activity-dependent mechanisms that have been collectively termed metaplasticity have evolved to help implement these essential computational constraints. Various intercellular signalling molecules can trigger lasting changes in the ability of synapses to express plasticity; their mechanisms of action are reviewed here, along with a consideration of how metaplasticity might affect learning and clinical conditions.

Long-term potentiation
(LTP). A long-lasting and activity-dependent increase in synaptic efficacy. Canonically it requires activation of the NMDAR subtype of glutamate receptors; however, different forms of LTP caused by the activation of other receptor subtypes also occur.

Long-term depression
(LTD). The converse of LTP: in LTD there is a long-lasting and activity-dependent decrease in synaptic efficacy.

Excitotoxicity
Cellular toxicity involving the activation of glutamate receptors in the CNS. Excessive activation of these receptors by high concentrations of glutamate or by neurotoxins leads to cell death.

Tetanus
A bout of HFS used to elicit activity-dependent synaptic plasticity. The frequency and duration of the stimulation varies across protocols.

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The ability of neurons to modify their structure and function as a result of activity is critical for normal development, learning and responding to brain damage and neurological disease. At the synaptic level, neural activity can generate persistent forms of synaptic plasticity, such as long-term potentiation (LTP) and long-term depression (LTD). There is now a wealth of data indicating that LTP and LTD mechanisms are used to retain new information in activated networks of neurons[1,2]. Safeguards must therefore be in place to prevent the saturation of LTP or LTD, which could ultimately compromise the ability of networks to discriminate events and store information and, in the case of extreme levels of LTP, lead to excitotoxicity.

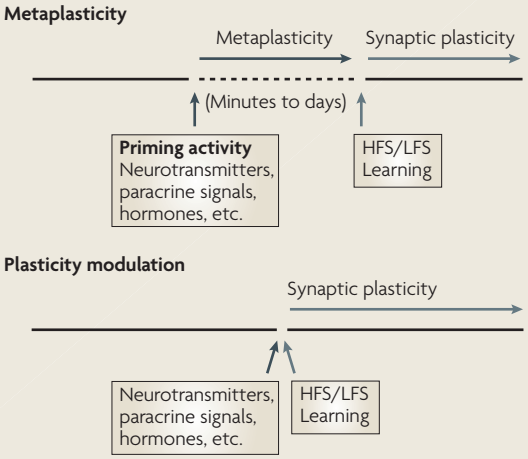
How is the proper balance of LTP and LTD maintained? Various intercellular signalling molecules — including catecholamines, GABA (γ-aminobutyric acid), acetylcholine, cytokines and hormones — directly regulate the degree of LTP and LTD that can be induced. However, a different kind of regulation that persists across time also exists. Here, neural activity at one point in time can change cells or synapses such that their ability to exhibit LTP or LTD after a later bout of activity is altered. This form of plasticity regulation has been termed metaplasticity[3,4]. The 'meta' part of the term reflects the higher-order nature of the plasticity — that is, the plasticity of synaptic plasticity.

Essentially, metaplasticity entails a change in the physiological or biochemical state of neurons or synapses that alters their ability to generate synaptic plasticity. A key feature of metaplasticity is that this change outlasts the triggering (priming) bout of activity and persists at least until a second bout of activity induces LTP or LTD (BOX 1). This distinguishes metaplasticity from more conventional forms of plasticity modulation in which the modulating and regulated events overlap in time. Metaplasticity entails an extensive range of mechanisms, many of which overlap with the mechanisms of conventional plasticity. This overlap, plus the fact that plasticity and metaplasticity can be induced simultaneously, poses a considerable challenge for metaplasticity research in terms of experimental design and interpretation. Nonetheless, there has been substantial progress in understanding metaplasticity over the past decade. In this Review, paradigms for inducing metaplasticity and other associated mechanisms will be detailed, followed by a consideration of the behavioural and clinical implications of these processes.

NMDA-receptor-mediated metaplasticity

A common paradigm for experimentally inducing metaplasticity involves pharmacological or synaptic activation of NMDA (*N*-methyl-D-aspartate) receptors (NMDARs). NMDAR activation is a key trigger for LTP induction; however, it has also been shown to trigger metaplastic changes that inhibit subsequent induction of LTP[5–8] (FIG. 1a). This effect is restricted to the activated synapses and slowly decays over 60–90 minutes[5]. The capacity to induce LTP can be recovered by increasing the tetanus stimulus intensity, indicating that the NMDAR priming stimulation elevates the threshold for LTP rather than completely inhibiting it[5]. However, even when LTP is induced by strong or repeated tetanic stimulation, priming synaptic activity can inhibit its persistence[8,9]. The inhibition of LTP by priming synaptic activity depends on the activation of NMDARs, adenosine A2 receptors, p38 mitogen-activated protein kinase (p38 MAPK) and the protein phosphatases 1A, 2A and calcineurin[8–11]. Importantly, the inhibition of LTP cannot be explained as simply a saturation of potentiation

Box 1 | **Methodological considerations in metaplasticity research**



The standard paradigm for studying metaplasticity is to have an episode of priming activity at one point in time and then a subsequent plasticity-inducing event, such as low-frequency stimulation (LFS), high-frequency stimulation (HFS) or learning, that evokes synaptic plasticity such as long-term potentiation (LTP) or long-term depression (LTD). The priming signal can entail electrical stimulation of neural activity, pharmacological activation of specific transmitter receptors, or behavioural events that might cause hormone release in addition to neural activity. An essential aspect of this protocol is that there must be a change in neural function as a result of the priming that persists after the termination or washout of the priming stimulus and that alters the response to a subsequent plasticity-inducing event (see figure, top). This distinguishes metaplasticity from conventional modulation of plasticity, whereby the modulation occurs in conjunction with the induction of plasticity (see figure, bottom). There is no agreed criterion for the degree of persistence that is required to meet the definition of metaplasticity, but commonly studied effects have ranged from minutes to many days.

The study of metaplasticity is facilitated when the priming stimulation does not overtly alter the strength of synaptic transmission, but instead changes only the state of readiness of synapses to generate LTP or LTD later on. If the priming stimulation does cause, for example, LTP, this makes it ambiguous whether a lack of further LTP induction by an HFS is due to a ceiling for LTP having been reached (termed saturation) or due to the mechanisms that generate LTP being actively inhibited. The situation also becomes ambiguous if such priming facilitates subsequent response depression, because it then needs to be ascertained whether LTD is being facilitated[183] or whether the synapses have simply become capable of exhibiting depotentiation[184]. Because LTD and depotentiation entail at least partially dissociable mechanisms[185], it greatly simplifies the analysis of LTD priming if prior LTP has not been induced and therefore depotentiation is not possible.

Unfortunately for investigators, it is probable that bouts of neural activity often cause both synaptic plasticity and metaplasticity. Protocols that induce LTP can also trigger metaplastic mechanisms that inhibit further LTP[34], and LFS can evoke a metaplastic lowering of the LTD threshold early in the stimulus train that is necessary for LTD induction[16]. This can complicate the interpretation of molecular correlates of plasticity, such as gene expression and protein synthesis, because in principle these events might be critical for synaptic plasticity, metaplasticity or both.

processes by the priming stimulation[12], as it can occur even when the priming stimulation does not cause any detectable change in basal synaptic transmission[5,8,13].

NMDAR activation can also facilitate the subsequent induction of LTD[14] (FIG. 1a). The LTD facilitation can be generated by low-frequency priming stimulation[14,15], is restricted to the activated synapses and lasts for 60–90 minutes *in vitro*[16] (it lasts longer *in vivo*[14]). The effect of priming on LTD can occur rapidly enough to contribute to the induction of LTD by conventional low-frequency stimulation (LFS) protocols[16]. Again, the priming stimulation can facilitate LTD without itself causing persistent synaptic plasticity.

The expression mechanisms that underlie NMDAR-mediated metaplasticity are not well understood. It has been reported that prior induction of LTP reduces the postsynaptic voltage threshold for subsequent LTD and elevates it for further LTP[17], but it is not clear what mechanisms mediate these effects or whether similar changes occur following non-plasticity-inducing priming stimulation.

It has been suggested that NMDAR activation results in LTD of NMDAR currents (LTD_{NMDAR}), which are crucial for the induction of conventional LTD and LTP and are known to be highly plastic in their function and localization (for reviews, see REFS 18,19). In support of this hypothesis, both LFS and low-frequency uncaging of glutamate at single dendritic spines cause LTD_{NMDAR} and a reduction in Ca^{2+} entry through the receptor channels[20–22]. Both nitric oxide (NO) and protein kinase C (PKC) mediate the LTD_{NMDAR}. These findings are supported by the fact that NMDAR activation increases NO production, which can in turn suppress NMDAR currents[23,24], and by the fact that pharmacological activation of PKC by phorbol esters causes a dispersal of NMDARs from synaptic to extrasynaptic sites[25,26], which might also be a prelude to receptor endocytosis[19,27]. Both NO and PKC have been linked to NMDAR-mediated metaplasticity[23,28–31], as has p38 MAPK[31,32].

Despite the attractiveness of this hypothesis, there is no direct evidence that LTD_{NMDAR} mediates metaplastic inhibition of LTP. Furthermore, other mechanisms are almost certainly involved. For example, the apparently NMDAR-dependent saturation of LTP by repeated high-frequency stimulation (HFS) protocols actually reflects an inhibition of further LTP, which can be recovered by using stronger stimuli during the HFS[33], by waiting for the metaplasticity to decay[34] or by stimulating β-adrenergic receptors[35]. This form of metaplasticity is not mediated by NO or by a reduction in NMDAR currents[35].

Downstream of NMDAR activation there are many other potential sites of metaplasticity expression. Ca^{2+}-dependent kinases and phosphatases are central to plasticity processes, and priming stimulation could alter the

Uncaging
The release of a molecule from a photolabile binding partner known as a cage. Cages typically inhibit the biological activity of the bound ('caged') molecule. A brief flash of light of the appropriate wavelength can photochemically disrupt the structure of the binding partner and render the now uncaged molecule biologically active.

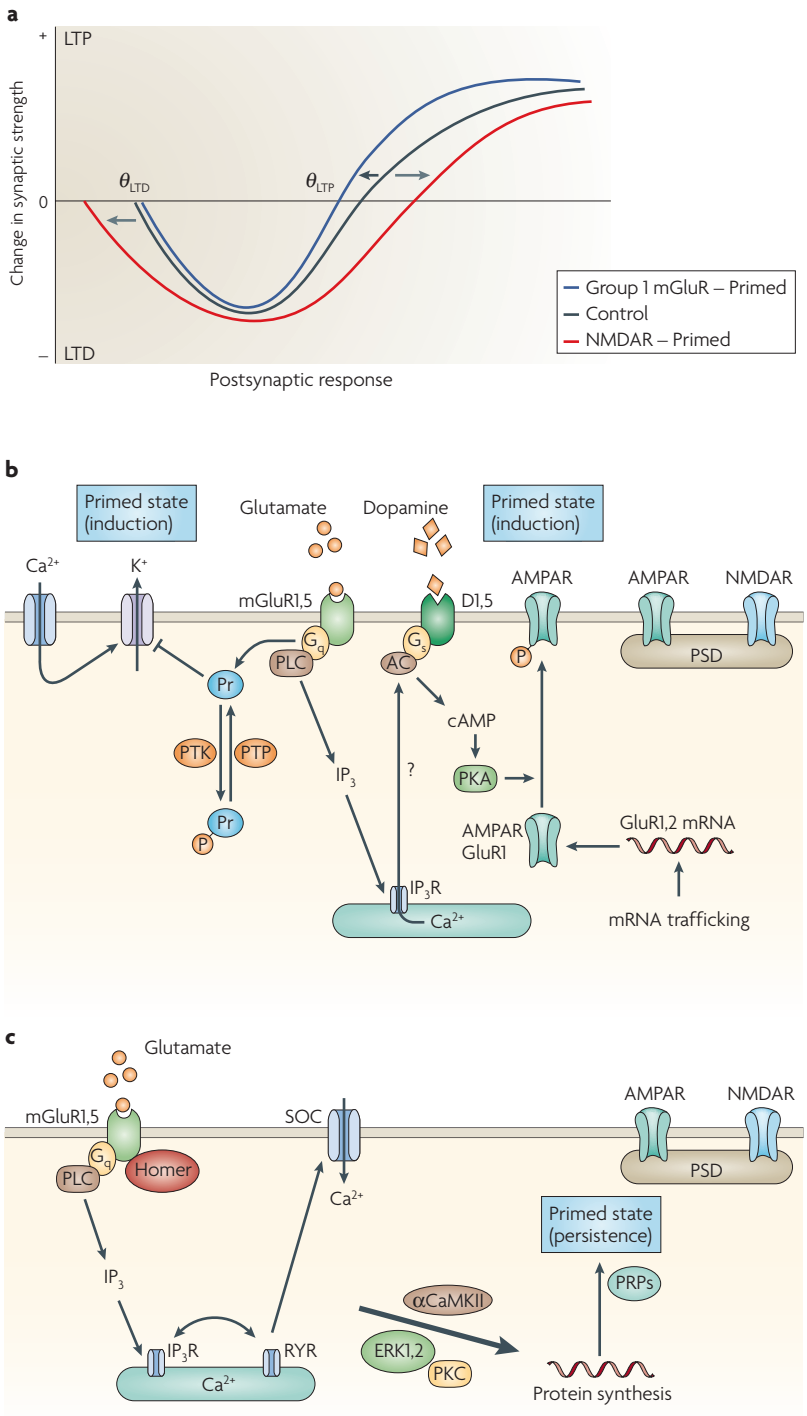


Figure 1 | **Glutamate-receptor-mediated mechanisms of metaplasticity. a** | The black (control) line shows how synaptic strength changes in response to afferent activity at different levels of postsynaptic cell firing at excitatory synapses on hippocampal CA1 pyramidal cells. θ_{LTD} and θ_{LTP} represent the threshold level of postsynaptic firing that is required in order for afferent stimulation to result in long-term depression (LTD) or long-term potentiation (LTP), respectively (see BOX 2). The effects of prior glutamate receptor activation (priming) on subsequent LTP and LTD are shown in blue and red. NMDA (*N*-methyl-D-aspartate) receptor (NMDAR) activation (red line) lowers the threshold for LTD (θ_{LTD}) while raising the threshold for LTP (θ_{LTP}), as shown by the grey arrows. By contrast, group 1 metabotropic glutamate receptor (mGluR) activation (blue line) lowers θ_{LTP}, as shown by the black arrow. **b** | Two mechanisms that have been suggested to mediate the metaplastic effects of metabotropic receptor activation on LTP induction. In the first, mGluR activation inhibits the Ca^{2+}-activated K^+ channel that mediates the slow after-hyperpolarization. This mechanism is regulated by the Tyr phosphorylation state of an unknown regulatory protein (phosphoprotein; Pr). In the second, adenylyl cyclase (AC) and protein kinase A (PKA) are activated by either stimulation of phospholipase C (PLC) by mGluR and subsequent release of Ca^{2+} from intracellular stores or, more directly, by dopamine D1 or D5 receptor activation of the G_s signalling pathway. Activation of PKA causes it to phosphorylate Ser845 of GluR1, a step which is necessary for GluR1-containing AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors (AMPARs) to be inserted into the extrasynaptic membrane. The enhancement of AMPAR-subunit mRNA trafficking to synaptic sites might also assist this process. **c** | Mechanisms that have been suggested to mediate the effects of group 1 mGluR activation on the synaptodendritic synthesis of plasticity-related proteins (PRPs), leading to enhanced LTP persistence. Evidence suggests that this process is mediated by the stimulation of PLC and the subsequent release of Ca^{2+} from intracellular stores (especially through ryanodine receptors (RYRs), which might be tethered to mGluR sites by Homer1). This Ca^{2+} release is supplemented by Ca^{2+} entry into the cell through store-operated channels (SOCs) in the plasma membrane. These processes trigger the activation of kinases such as extracellular-signal-regulated kinase 1 (ERK1), ERK2, protein kinase C (PKC) and α-calcium/calmodulin-dependent protein kinase II (αCaMKII), which contribute to the activation of local protein synthesis machinery. The identity and function of the PRPs are still being elucidated. cAMP, cyclic AMP; G, G protein; IP_3, inositol trisphosphate; IP_3R, IP_3 receptor; PSD, postsynaptic density; PTK, phosphotyrosine kinase; PTP, phosphotyrosine phosphatase.

magnitude or duration of the increase in the intracellular free Ca^{2+} concentration during plasticity induction, leading to altered enzyme activity[3,36,37]. More experimental attention, however, has been given to the effects of priming on the phosphorylation state of key Ca^{2+}-dependent kinases, such as α-calcium/calmodulin-dependent protein kinase II (αCaMKII)[38,39], which has a critical role in initiating LTP by regulating AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor (AMPAR) conductance and transport to the membrane[40]. Mutation of Thr286 of αCaMKII to Ala mimics the autophosphorylated state of αCaMKII (in which its activity is Ca^{2+}-independent) and replicates the effects of NMDAR priming stimulation[41]. Such autophosphorylation might account for the apparent saturation of LTP following HFS, as LTP is accompanied by a prolonged increase in CaMKII autophosphorylation at Thr286 (REF. 42). It is not clear, however, whether autophosphorylation of Thr286 can be elicited by priming stimulation that does not itself cause LTP. The functional contribution of Thr286 autophosphorylation to metaplasticity also remains unclear. It could, for example,

trap calmodulin and prevent it from activating other enzymes. Indeed, knocking out another binding partner of calmodulin, RC3 (also known as neurogranin), led to a decrease in the LTP threshold[43].

An alternative αCaMKII autophosphorylation site that might mediate the inhibition of LTP is Thr305/Thr306. Priming stimulation of lateral perforant path synapses in the dentate gyrus prevented subsequent LTP induction for up to 18 hours, without affecting LTD[44]. Mutation of Thr305/Thr306 to prevent αCaMKII autophosphorylation at these sites completely blocked the metaplasticity. The mutation did not affect metaplasticity in medial perforant path synapses, consistent with the lack of dependence of LTP on αCaMKII in this input pathway[45].

mGluR-mediated metaplasticity

In contrast to the inhibitory effects of NMDAR priming on LTP, activation of group 1 metabotropic glutamate receptors (mGluRs) facilitates both the induction and the persistence of subsequent LTP in area CA1 (FIG. 1a). The increased induction is not input specific and seems to be mediated in part by a long-term downregulation of the Ca^{2+}-activated K^+ current that underlies the slow afterhyperpolarization (slow AHP)[46]. This has the effect of enhancing the level of depolarization that is reached during HFS (FIG. 1b). The reduction in the slow AHP is mediated by a non-classical mGluR signalling pathway that does not involve phospholipase C (PLC), PKC or the release of Ca^{2+} from intracellular stores[47], but which is regulated by the degree of Tyr phosphorylation of one or more unknown regulatory proteins[48] (FIG. 1b).

The enhancement of LTP induction by mGluR activation might also be mediated by increased trafficking of AMPARs to the extrasynaptic membrane as a result of PKA-mediated phosphorylation of Ser845 of the GluR1 subunit[49,50]. This primes the AMPARs for entry into and capture in the postsynaptic density during subsequent synaptic activity. This priming process could be amplified by mGluR-triggered trafficking of the mRNA for the AMPAR subunits GluR1 and GluR2 into dendrites, which would expand the pool of receptors that are available for later insertion[51] (FIG. 1b).

mGluR activation might also facilitate NMDAR function or trafficking, as many G-protein-coupled receptors (GPCRs) are known to amplify NMDAR currents[52,53]. Indeed, activation of muscarinic and corticotropin-releasing factor receptors, which initiate a signalling cascade that is similar to that which is initiated by group 1 mGluRs, can also prime hippocampal LTP[54–56]. However, preliminary analysis has suggested that an increase in NMDAR function is not responsible for the priming of LTP by mGluRs[57]. In the prefrontal cortex, GPCR facilitation of subsequent LTP entails dopamine D1 and D2 receptor activation in concert with NMDAR activation[58]. The mechanisms that are involved in this form of metaplasticity include D1-receptor-triggered delivery of GluR1-containing AMPARs to the extrasynaptic membrane[59] (FIG. 1b).

Independent of its enhancement of LTP induction, group 1 mGluR activation can also facilitate the persistence of LTP. For example, HFS of group 1 mGluRs sets a 'molecular switch' that abrogates the need for these receptors to be activated during subsequent stimulation in order to generate persistent LTP[60]. The priming stimulation affects LTP only at primed synapses and lasts for at least an hour[61]. The signalling cascade that is involved in this switch-setting includes the activation of mGluR5, αCaMKII and PKC[62–64].

Similarly, prior pharmacological or HFS priming of group 1 mGluRs — which by itself does not notably affect synaptic efficacy — converts a decaying form of LTP into a longer lasting form[55,57,65], an effect that is particularly prominent in the ventral hippocampus[66]. The effects of this priming stimulation are mediated by the activation of PLC[55], the release of Ca^{2+} from intracellular stores and the entry of Ca^{2+} through store-operated Ca^{2+} channels in the plasma membrane[66,67] (FIG. 1c). Direct priming activation of the ryanodine receptors that regulate Ca^{2+} release from intracellular stores also facilitates subsequent LTP[67]. Ultimately, these pathways lead to the stimulation of local protein synthesis at the synapse[65], with the newly synthesized proteins being kept in reserve for enhancing the persistence of subsequently generated LTP. The pathway that leads from mGluR stimulation to local protein synthesis probably entails activation of the protein kinase mammalian target of rapamycin (mTOR), which facilitates the translation of terminal oligopyrimidine mRNAs[68], as this pathway is also triggered during mGluR-dependent LTD[68] and during a protein-synthesis-dependent late phase of LTP[69]. Although it is not clear which newly synthesized proteins contribute to the priming of LTP, candidates include elongation factor 1α[70], αCaMKII[71], elongation factor 2, ribosomal protein S6 and poly-A binding protein 1 (REF. 69).

Priming stimulation of mGluRs affects the plasticity of medial perforant path synapses in the dentate gyrus, but the effects are opposite to those described above for CA1. In the dentate gyrus, prior activation of group 1 or group 2 mGluRs by HFS inhibits subsequent LTP by activating PKC and p38 MAPK mechanisms[31]. Under these conditions, the mGluRs might merely be amplifying the function of NMDARs, which also contribute to the inhibition of LTP[31]. Priming HFS also inhibits mGluR-dependent LTD at these synapses, again through group-1-mGluR- and PKC-dependent mechanisms, but independently of NMDARs[72].

Heterosynaptic metaplasticity

The metaplasticity examples described above are largely homosynaptic in nature; that is, the synapses that are activated during the priming stimulation are also those that show altered plasticity. However, activity at one set of synapses can also affect subsequent plasticity at neighbouring synapses. Such heterosynaptic metaplasticity was predicted by the Bienenstock, Cooper and Munro computational model of synaptic plasticity[73] (BOX 2), in which cell-wide modifications in the threshold for LTP induction are driven by the history of postsynaptic cell firing.

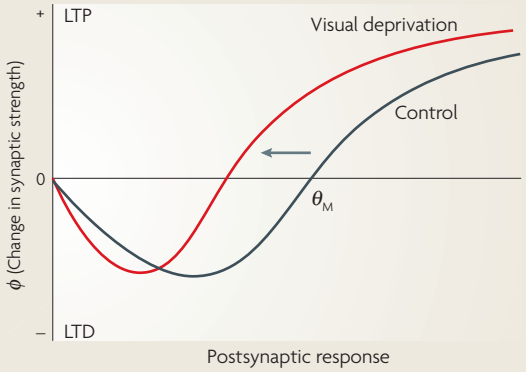
Studies in the hippocampus have begun to reveal a complex variety of heterosynaptic interactions that govern LTP induction and persistence. In CA1 *in vitro*,

Calcium/calmodulin-dependent protein kinase II (CaMKII). A multi-functional serine/threonine kinase that is activated by a Ca^{2+}/calmodulin complex. Once activated, CaMKII can autophosphorylate, leading to autonomous (Ca^{2+}-independent) activity and calmodulin trapping. The α isoform is a major component of the postsynaptic density and a key component of the LTP induction process.

Slow afterhyperpolarization (slow AHP). A type of membrane hyperpolarization that can last for seconds. It is mediated by the opening of Ca^{2+}-dependent K^+ channels and is generated in response to the firing of one or more postsynaptic Na^+ or Ca^{2+} action potentials.

G-protein-coupled receptors (GPCRs). A large family of transmembrane receptors that couple extracellular signalling molecules to an intracellular signalling cascade which they trigger by activating a G protein.

Box 2 | **The Bienenstock, Cooper and Munro model**



The Bienenstock, Cooper and Munro (BCM) computational model of synaptic plasticity was developed to account for experience-dependent plasticity in the kitten visual cortex[73]. Subsequently it has been adapted to account for experience-dependent plasticity in the adult rat barrel cortex and long-term potentiation (LTP) and metaplasticity in the adult rat dentate gyrus[186,187].

The model has two principal features. First, it describes the extent of LTP or long-term differentiation (LTD) as a function (ϕ) of the degree of postsynaptic cell firing during afferent activation (see figure). If afferents are active during times of low postsynaptic activity, those inputs are depressed. Conversely, if afferents are active during high postsynaptic activity, those inputs are potentiated. To preserve stability in the network and prevent runaway potentiation or depression, the model incorporates a feature that varies the crossover point between LTD and LTP on the ϕ function, termed the modification threshold (θ_M), with the time-averaged level of postsynaptic firing. Thus, if firing levels are maintained at a high level, the modification threshold shifts to the right, making LTP harder to obtain and LTD easier to obtain. More recent models have combined BCM principles with experimentally observed features of spike-timing-dependent plasticity, whereby the precise timing of action-potential firing relative to the synaptic activation determines the direction and degree of synaptic modification[186,188].

Although cell firing is the key computational unit of the BCM model, it has been suggested that the physiological metric used for computing weight changes could be the level of intracellular free Ca^{2+}, as Ca^{2+} is a key trigger for both LTP and LTD induction[36,189]. Subsequently, wholly Ca^{2+}-based models have been generated by Cooper and colleagues, with particular emphasis on the role that NMDARs have in generating the relevant Ca^{2+} signals[190,191]. The resulting Ca^{2+}-dependent plasticity model, like the BCM model, accounts for many aspects of LTP and LTD induction. Importantly, it also features homeostatic metaplasticity, which is generated by slow, activity-dependent changes in the regulation of intracellular Ca^{2+} levels[193].

strong priming stimulation of one input pathway facilitated the induction of LTD (and depotentiation) and inhibited the induction of LTP in a neighbouring set of synapses[74,75]. This modulation lasted 90–150 minutes and was not blocked by administration of the NMDAR antagonist 2-amino-5-phosphonovaleric acid (APV) during the priming stimulation[74]. A similar effect, which was also observed in CA1, required extensive stimulation of the priming pathway and extensive activation of NMDARs and voltage-dependent Ca^{2+} channels[76]. The molecular mechanisms that mediate such heterosynaptic inhibitory actions have not yet been investigated.

In the dentate gyrus *in vivo*, the induction of LTP in medial perforant path synapses inhibited subsequent LTP in nearby lateral perforant path synapses, an effect that lasted for more than 2 days[77]. In accord with predictions of the BCM model, simply applying antidromic stimulation to the postsynaptic granule cells in the presence of an NMDAR antagonist was sufficient to block LTP. These results suggest that a cell-wide homeostatic process adjusts plasticity thresholds to keep the overall level of synaptic drive to a neuron within a range that permits plasticity to be expressed.

Synaptic tagging and capture. Despite the apparent theoretical advantages of restraining the overall amount of LTP that a cell exhibits, there are nonetheless mechanisms that mediate cooperative and metaplastic upregulation of the persistence of LTP and LTD. Normally a weak HFS cannot generate the protein-synthesis-dependent late phases of LTP. However, if a strong HFS that induces protein-synthesis-dependent LTP in one input pathway precedes a weak HFS to a second, independent pathway, this enables the second pathway to establish a late phase of LTP[78] (FIG. 2). This process is referred to as synaptic tagging[79]; molecules in the synapses of the second pathway are said to be tagged by the weak stimulation in a way that permits them to capture the proteins that have been synthesized in response to stronger stimulation elsewhere.

Synaptic tagging is also effective when the regulating event (the strong HFS) follows the test event (the weak HFS), in which case the temporal ordering of events does not fit a metaplasticity paradigm. Nevertheless, this shows that synaptic tags can be maintained for several hours post-HFS[78], although *in vivo* they might last for less than 30 minutes[80]. The tag can be deleted by LFS shortly after it is set[81], or can be prevented from being set by prior LFS[82] (FIG. 2). The latter protocol affects LTP maintenance both homosynaptically and heterosynaptically and depends on the activation of the protein phosphatases 1A and 2A, which reduces the ability of PKA to participate in tag-setting[83,84]. Important issues that remain to be resolved are the identities of the newly synthesized plasticity-related proteins (PRPs), how these proteins are captured by the tagged synaptic proteins and how they promote LTP persistence. Recently a constitutively active PKC isoform, protein kinase Mζ, was identified as a key PRP. Inhibiting this kinase completely reversed LTP that was made persistent by the tag-and-capture process[85]. Synaptic tagging and capture also occur for the late phase of LTD[86]. Remarkably, it seems not to matter whether late-phase LTD or late-phase LTP are induced in the first pathway, as either protocol can

Depotentiation
A reversal of LTP that brings synaptic efficacy to a baseline level. There is growing evidence that this process involves mechanisms that are different to those that mediate LTD.

Antidromic stimulation
The activation of neuronal cell bodies and dendrites by back-propagating action potentials triggered by electrical stimulation of the cells' axons.

Plasticity-related proteins
(PRPs). Proteins that are synthesized in response to synaptic activation or postsynaptic activity and that are necessary for establishing the persistent forms of LTP and LTD.

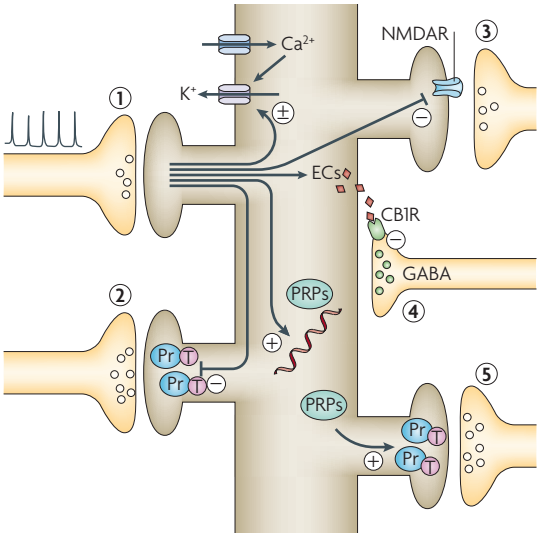


Figure 2 | **Proposed mechanisms of heterosynaptic metaplasticity.** Priming activity at excitatory synapse 1 has the potential to cause lasting inhibition or facilitation of the Ca^{2+}-activated K^+ channel mediating the slow after-hyperpolarization (top); to inhibit setting of the synaptic 'tag' by a subsequent high-frequency stimulus (synapse 2); to inhibit NMDA (*N*-methyl-D-aspartate) receptor (NMDAR) function (synapse 3); to trigger the production and release of endocannabinoids (ECs), which cause a presynaptic inhibition of GABA (γ-aminobutyric acid) release at inhibitory terminals (synapse 4); and to activate the synthesis of plasticity-related proteins (PRPs), which are captured by the synaptic tags that are set by a subsequent HFS at neighbouring synapses, facilitating the persistence of the otherwise-decaying long-term potentiation produced there (synapse 5). CB1R, cannabinoid receptor 1; Pr, protein; T, tag.

support the development of the late phase of subsequent LTP or LTD in the second pathway[87].

The effects of synaptic tagging are confined to local dendritic compartments. Thus, protein synthesis that is stimulated in basal dendrites does not promote LTP or LTD persistence in the apical dendrites of CA1 pyramidal cells[84], presumably because the proteins are generated synaptodendritically and not somatically[88] unless very strong stimuli are used[89,90]. This dendritic compartmentalization has been proposed to offer computational advantages for memory formation[88]. Conversely, somatically synthesized proteins can protect LTP from depotentiation in a cell-wide fashion[91].

Heterosynaptic metaplasticity that promotes LTP has also been observed in the dentate gyrus of whole animals. Stimulation of extrinsic inputs, such as those that originate from the basolateral amygdala (BLA), up to 15 minutes before HFS of the perforant path can facilitate the induction and persistence of LTP[80,92], as well as the induction of LTD[93]. The facilitated persistence of LTP is protein-synthesis-dependent and is mediated by the activation of cholinergic systems in the medial septum and β-adrenergic systems arising from the locus coeruleus[80,94,95]. The facilitation is itself regulated by the history of prior BLA stimulation[93]. As for tagging and capture, BLA stimulation can reinforce late-phase LTP if it is given after the weak HFS of the perforant path or if it is given beforehand[80], indicating that PRPs can be captured at any time as long as the key synaptic molecules remain tagged.

Metaplasticity arising from changes in cell excitability. As both LTP and LTD are depolarization-dependent, heterosynaptic metaplasticity might arise from changes in the membrane properties or excitability of the post-synaptic neuron. Activity-dependent alterations in the properties or levels of voltage-dependent Na^+, Ca^{2+}, Cl^- and K^+ channels have been reported (for recent reviews, see REFS 96–98), and the resultant modification of cell excitability has been termed intrinsic plasticity[96]. Although intrinsic plasticity is likely to be an important memory mechanism in its own right[99], it is also strongly predicted to be a metaplasticity mechanism that regulates LTP and LTD, given the effects that ion channels have on transmitter release, postsynaptic depolarization, the delivery of back-propagating action potentials to the dendrites and the triggering of protein synthesis and gene expression.

Although demonstrations of the metaplastic effects of intrinsic plasticity are rare, progress is being made towards establishing these effects' existence. Ca^{2+}-dependent K^+ channels in the postsynaptic membrane that underlie post-spike AHPs are good candidates for study because they regulate the threshold for LTP induction in many neurons[100] (FIG. 2). Pharmacological activation of β-adrenergic receptors or group 1 mGluRs can elicit long-lasting reductions in these AHPs, lowering the threshold for LTP induction[46]. It has been difficult, however, to demonstrate long-term reductions in channel function following synaptic stimulation, although HFS of afferents led to an NMDAR-dependent and cyclic-AMP/PKA-mediated suppression of the slow AHP in hippocampal pyramidal cells[101]. This suppression lasted for a few minutes and was associated with facilitation of LTP induction. By contrast, HFS in one study was found to cause a long-term amplification of the slow AHP that was associated with the inhibition of subsequent LTP both homo- and heterosynaptically[102].

Other channels that should attract attention include the A-type K^+ channel and the hyperpolarization-activated cation channel that mediates the non-selective cation current, I_h, as both regulate LTP and LTD and both show long-term reductions in function following synaptic stimulation[103,104].

There is now widespread appreciation that the excitatory inputs onto GABAergic interneurons can undergo multiple forms of LTP and LTD, generating changes in inhibition onto principal cells[105–107]. Although it is debatable whether plasticity of GABAergic signalling *per se* is a type of metaplasticity, when postsynaptic excitation leads to a direct retrograde regulation of neighbouring GABAergic afferent terminals then its designation as a metaplasticity mechanism becomes more clear-cut. Indeed, both evoked and spontaneous presynaptic release of GABA are transiently inhibited by postsynaptic depolarization or cell firing, in a process termed

Back-propagating action potentials
Action potentials that are initiated at the soma or the axon hillock and that propagate back into the dendrites, where they shape the integration of synaptic activity and influence the induction of synaptic plasticity.

depolarization-induced suppression of inhibition (DSI)[108] (FIG. 2). Such plasticity is likely to powerfully affect the synchrony of cell firing and information processing in neuronal networks. Moreover, it should affect the plasticity of excitatory synapses on the principal neurons, as GABAergic inhibition profoundly affects plasticity thresholds[109,110].

Both DSI and its longer-term counterpart, inhibitory LTD (iLTD) of GABA release (which persists for more than an hour), are mediated by the activation of presynaptic cannabinoid 1 (CB1) receptors on the GABA terminals. These receptors are activated by endogenous endocannabinoids that serve as retrograde signals following postsynaptic group-1 mGluR activation and membrane depolarization[111–114] (FIG. 2). During the minute or so that DSI persists, LTP induction at excitatory inputs is facilitated[115]. Similarly, priming-stimulation-induced iLTD facilitates LTP that is induced at least 60–90 minutes later[116,117]. This latter form of metaplasticity entails mechanisms that are distinct from those that are at work in DSI, including CB1-receptor-mediated activation of presynaptic cAMP/PKA signalling and presumed phosphorylation of the active zone protein Rab3-interacting molecule 1α (Rim1α)[116,118]. Intriguingly, focal-stimulation experiments revealed that the spatial spread of iLTD, and thus the facilitation of LTP, extended 10–40 μm from the excitatory synapses that were stimulated during priming[117]. This mechanism seems to be well-suited for promoting bands of localized LTP on the dendrites of postsynaptic neurons[88,119]. It could also be an important mediator of the mGluR-mediated priming of LTP described above, although other mechanisms must also contribute because mGluR priming is observable in the presence of the $GABA_A$ antagonist picrotoxin[57].

Behavioural relevance of metaplasticity

Metaplasticity induced by environmental stimuli. Environmental stimuli, such as enriched environments or stressful events, can powerfully affect synaptic plasticity. Such regulation could in principle be considered a form of metaplasticity. However, it is often difficult to distinguish modulation of plasticity, generated by the presence of released hormones, catecholamines or neurotrophic factors, from metaplasticity. One approach is to use *ex vivo* experimental preparations, in which tissue is removed from environmentally stimulated animals and studied *in vitro*. This approach has shown that enriched-environment exposure or exercise can facilitate LTP induction and persistence[120,121], although others have reported an apparent inhibition of LTP that was due to occlusion by environmentally induced LTP[122]. Intensely stressful stimuli, such as restraint or tail-shock, reliably inhibit hippocampal LTP and facilitate LTD[123]. These effects can be observed for up to 24 hours after the stressful experience[124] and can be blocked by giving systemic NMDAR antagonists at the time of the stressful experience[123]. Remarkably, the same stressor can both inhibit LTP through glucocorticoid receptor activation in the dorsal hippocampus and facilitate LTP through mineralocorticoid receptor activation in the ventral hippocampus[125].

Is the inhibition of LTP by stress a metaplastic effect or simply an occlusion of further LTP by stress-induced LTP[126–129]? Evidence that it might be the latter is provided by the fact that strong fear conditioning leads to a potentiation of responses that lasts for up to 7 days in CA1 (REF. 130) and for at least 24 hours in the cerebellum[131]. However, as the inhibition of LTP in CA1 lasted for only 1 day[132] whereas the response potentiation persisted for 7 days, it seems that response potentiation *per se* is not sufficient to account for the lack of further LTP in the hippocampus. This suggests that a simultaneous induction of NMDAR-mediated LTP and metaplasticity prevents further LTP.

Developmental metaplasticity in the visual cortex. Dark rearing can reduce the thresholds for LTP and LTD in visual cortical neurons[133,134]. Exposing dark-reared animals to light for 2 days completely reverses these effects[133], which might be mediated at least in part by an experience-dependent switch in NMDAR subunit composition. Early in life, NR2B is the predominant NR2 subunit of NMDARs in the visual cortex[135]. During normal developmental maturation through the critical period, NR2A subunits become more prominent[135]. In dark-reared animals this maturational change is reduced, but 2 hours of light exposure is sufficient to markedly increase the proportion of NR2A-containing receptors[136]. An even faster activity-dependent switch in NMDAR subunit composition following tetanic stimulation has been reported in neonatal hippocampal neurons[137].

Because NR2A-containing receptors produce currents that are shorter than those that are produced by NR2B-containing receptors, and because they should thus be associated with reduced synaptic Ca^{2+} accumulation[138], the subunit composition of NMDARs was predicted to account for the effects of dark rearing and subsequent light exposure on plasticity thresholds. Indeed, pharmacological agents that mimicked the effects of light exposure on dark-reared rats by shortening NMDAR currents also reproduced the elevation in LTD threshold[134], whereas NR2A-knockout mice lost the capacity for visual experience to metaplastically regulate their plasticity thresholds[139]. The prominence of the subunit-switch hypothesis, however, does not rule out other development- and experience-dependent changes, such as altered levels of GABAergic inhibition, brain-derived neurotrophic factor or other modulatory agents, contributing to the metaplastic effects.

Learning-associated metaplasticity. A key issue is whether metaplasticity is important for learning. Does learning cause metaplasticity that influences either the current period of acquisition or the learning of new information in the future? Certainly stressful stimuli or enriched environments can affect synaptic plasticity in addition to learning and memory, but the link between learning and metaplasticity remains uncertain. There is growing evidence, however, that learning-induced long-term alterations in AHPs might directly affect new learning. It is now well established that reflex conditioning in invertebrates and mammals produces intrinsic plasticity

Active zone
A portion of the presynaptic membrane that faces the postsynaptic density across the synaptic cleft. It is the site of synaptic vesicle clustering and docking and resultant neurotransmitter release.

Critical period
A finite but modifiable developmental time window during which experience provides information that is essential for normal development and permanently alters brain structure and performance.

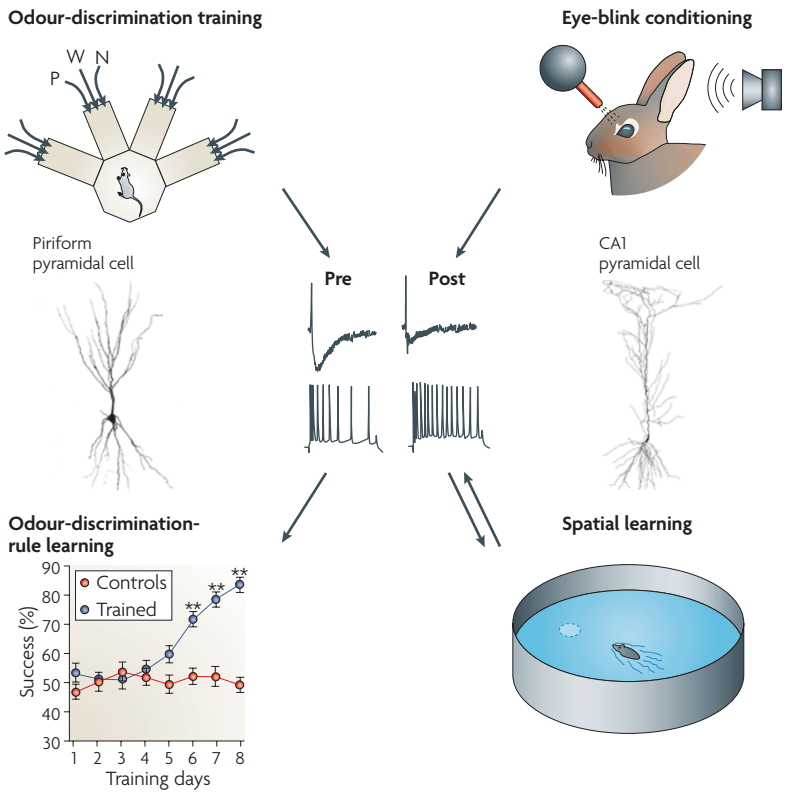


Figure 3 | **Proposals for metaplasticity that is induced during learning.** Training can induce a reduction of the slow afterhyperpolarization (slow AHP) and a corresponding increase in cell excitability. Odour-discrimination training can cause these effects to occur in both piriform and CA1 pyramidal cells and lead to a facilitation of odour-discrimination-rule learning as well as spatial-memory acquisition in the water maze. Eye-blink conditioning and spatial training in the water maze can also elicit these physiological changes in CA1 pyramidal cells. Such changes might be important for the early phases of learning in these tasks. However, other mechanisms are not excluded. The top left section of the figure depicts the odour-discrimination apparatus, including the odour ports P (the site of the rewarded stimulus) and N (the site of the non-rewarded stimulus) and the water-reward port (W). The bottom left section shows the acquisition of a response to the positive odour in the trained animals and no learning in the control pseudo-trained animals. The top waveforms illustrate the slow AHP pre-training (Pre) and how it might look after being reduced by training (Post). The bottom waveforms illustrate the corresponding increase in action-potential firing to a depolarizing-current pulse. The sections illustrating odour-discrimination training are modified, with permission, from REF. 151 © (2006) Oxford University Press. The piriform pyramidal cell was kindly provided by John Bekkers and Noromitsu Suzuki (Australian National University). The reconstructed CA1 pyramidal cell was kindly provided by Clarke Raymond (Australian National University).

Eye-blink conditioning
A classical conditioning paradigm that is commonly used for the study of learning. In it, an eye-blink, or the retraction of the nictitating membrane over the eye, is reflexively conditioned by pairing a conditioned neutral stimulus such as a tone with an aversive stimulus such as an air-puff to the eye. After sufficient pairings the conditioned stimulus can elicit the eye-blink response by itself.

of cell excitability[140–142]. In rabbit eye-blink conditioning, learning-induced reductions in the slow AHP and increases in cell firing in response to a depolarizing current pulse lasted for up to 5 days in CA1 pyramidal cells[143] (FIG. 3). These changes were not observed in animals that were given the same conditioned and unconditioned stimuli but in a random order. Similar effects have been reported in rat CA1 pyramidal cells following spatial water maze training[144] and in piriform cortical neurons after operant conditioning and olfactory-discrimination training[145,146], where a persistent decrease in the apamin-sensitive medium AHP was also observed[147] (FIG. 3). The persistent decrease in the slow AHP is mediated by a prolonged increase in PKC, extracellular-signal-regulated kinase 1 (ERK1) and ERK2 activity[146]. Curiously, at approximately the time that olfactory-discrimination learning reduces the slow AHP, there is a shift in plasticity thresholds in the olfactory cortex towards enhanced LTD and reduced LTP[148,149], as well as an increase in the NR2A/NR2B ratio for piriform NMDARs[149].

An increased slow AHP, which can, for example, be induced by aging and by increased levels of corticosterone, impairs learning and memory[150]. Similarly, it has been proposed that a reduction of the slow AHP might be critical for the learning process: it might metaplastically lower the threshold for LTP[150]. Moreover, the changed neuronal state that is represented by the reduced slow AHP might provide an improved environment for new learning. These concepts were lent support when olfactory-discrimination training was observed to reduce the slow AHP in rat CA1 pyramidal neurons of trained but not pseudo-trained animals[151]. The slow AHP reduction occurred before there was any behavioural evidence that the discrimination rule had been learned, and was reversed once the learning rule was acquired. Importantly, the ability to learn a different task for which CA1 cells are important — spatial navigation in a water maze — was enhanced during the time period that the slow AHP was reduced[151] (FIG. 3).

Another potential metaplasticity mechanism that might enhance the neuronal environment for learning can be inferred from the dependence of transcriptional processes on the state of histone acetylation and DNA methylation. Animals that have been trained on memory tasks show increased histone acetylation in relevant brain regions, and pharmacological inhibition of histone deacetylase promotes the formation of long-term memory and a late phase of LTP[152]. Conversely, inhibitors of DNA methylation block memory consolidation and inhibit the late phase of LTP[153,154]. These data suggest that the proteins that are synthesized as a result of learning-activated transcription might promote subsequent long-term memory formation in a new task, as long as there is overlap of the neurons participating in the learning of the two tasks and as long as the proteins produced during the first task can be captured by molecules tagged during learning of the second task.

In a different model, single-whisker stimulation generates NMDAR-dependent LTP of connections between layer 4 and layer 2/3 neurons in the barrel cortex[155]. Eventually potentiation stabilizes owing to NMDAR-dependent inhibition of LTP. However, additional whisker stimulation can increase responses further through a metaplastic recruitment of mGluR-dependent mechanisms, if the inhibitory effect of NMDARs is pharmacologically blocked[155]. These findings indicate that NMDAR inhibition and mGluR facilitation of LTP are in a dynamic balance and are regulated by sensory experience.

Clinical relevance

Learning and memory mechanisms lie at the heart of all cognitive functions, and synaptic plasticity is vital for normal cognition and behaviour. Not surprisingly, many

neurological disorders entail learning and memory deficits, and animal models of Alzheimer's disease[156], head injury[157,158], stroke[159], epilepsy[160], Down syndrome[161], Fragile X-linked mental retardation syndrome[162], Parkinson's disease[163] and Huntington's disease[164] all show evidence of dsyregulated synaptic plasticity. Furthermore, abnormal conditions such as prolonged inhibition of synaptic input can lead to alterations in synaptic receptor complement and ion-channel expression[165]. Insofar as these latter changes return neurons to a pre-existing level of activity, they can be viewed as being homeostatic in nature. However, as some changes include increased expression of Ca^{2+}-conducting glutamate receptors/channels, such as NMDARs and GluR2-lacking AMPARs, they could serve a metaplasticity function as well[19,166,167]. Hyperactivity during epilepsy also upregulates GluR2-lacking AMPARs, which might promote pathological levels of plasticity[168]. Therefore, it is important to understand regulatory mechanisms such as metaplasticity both to gain insight into disease mechanisms and to provide targets for promoting functional recovery and repair.

An excellent example of how metaplasticity might be harnessed for clinical purposes arose from studies of visual cortex plasticity, which have challenged the conventional wisdom that the adult visual cortex cannot exhibit the experience-dependent plasticity that is seen in juveniles. In fact, a nearly complete capacity for ocular dominance shifts is observed in the visual cortex following monocular visual deprivation (MD) when adult animals are given 7 days of dark exposure shortly before the MD[169]. Furthermore, prior experience with transient MD, either during development or as an adult, sensitizes the adult cortex to future bouts of MD, leading to more rapid and persistent changes[170]. Importantly, it has been reported that the loss of visual acuity (amblyopia) that is associated with chronic MD can be significantly reversed if the animals are given either 3–10 days of dark exposure before the return of vision to the occluded eye[171] or 2–3 weeks of enriched-environment exposure[172]. These effects presumably occur by reducing plasticity thresholds through a return to the juvenile (NR2B-containing) form of NMDARs and decreasing the inhibition–excitation ratio[169,172]. These exciting experiments suggest that metaplastic alteration of the threshold of cortical synapses for synaptic change might be a possible therapeutic approach to adult amblyopia.

Another consideration is that metaplasticity, by homeostatically preventing the saturation of synaptic potentiation, might guard against excitotoxicity or epilepsy. Indeed, synaptic or pharmacological stimulation of glutamate receptors can inhibit the subsequent induction of epileptic seizures[173,174]. Furthermore, some metaplasticity control mechanisms might be part of a larger repertoire of endogenous cellular mechanisms that protect against excitotoxicity and death — for example, those that are involved in ischaemic preconditioning (IPC) (for reviews, see REFS 175–177). The induction of IPC bears some similarity to a metaplasticity protocol and might entail overlapping signalling molecules and cellular processes, such as NMDARs, mGluRs, adenosine and protein synthesis. Also, both phenomena exhibit short-term (minutes–hours) and long-term (days) modes of operation. Accordingly, understanding the mechanisms that mediate metaplasticity might help us to generate new hypotheses regarding the molecular mechanisms of IPC and might help us to identify new therapeutic targets for experimental testing.

Implications for network function

Given how robust synaptic plasticity can be, there is a clear need for homeostatic controls, to prevent LTP from occurring too readily in response to weak stimuli or to too great an extent after strong stimuli, with possible resultant excitotoxicity. Conversely, metaplasticity can prevent a network from becoming incapacitated by too much LTD or by loss of afferent input[178]. Such controls have been predicted on theoretical grounds in network models and have been shown empirically to operate in practice.

An important implication of metaplasticity is that metaplasticity mechanisms can be operative even during plasticity induction. Thus, changes to plasticity thresholds early during an induction protocol might facilitate plasticity induction by later stimuli[16]. This seems to happen during learning as well[150,151]. Thus, metaplasticity mechanisms might begin to function relatively quickly after their engagement, in order to put synapses and networks into a learning-ready state. The possible co-engagement of metaplasticity and plasticity mechanisms renders it difficult to ascribe particular molecular changes induced by conditioning stimulation to one mechanism or the other. Protein synthesis, for example, can promote plasticity persistence (or memory consolidation) but can also raise the threshold for reversing the plasticity (the memory) as a metaplasticity mechanism. Subsequent stimulus patterns or, in the case of memory, environmental cues might then first have to lower the plasticity thresholds at these synapses before additional plasticity (learning) can occur. Thus, it needs to be clarified which proteins serve plasticity versus metaplasticity functions or, alternatively, whether the two outcomes derive from the activation of common effectors.

A third general contribution that metaplasticity might make is to the prolongation of memory retention. Models of dynamically learning neural networks have shown that incorporating multiple metaplastic states at the learning nodes of the model helps to keep previously learned information from being overwritten by new learning[179,180]. It is interesting to note, therefore, that in hippocampal organotypic cultures up to five discrete synaptic states have been described, with the number being dependent on both the degree of synaptic efficacy evident at the synapse and the history of prior activity that generated that level of efficacy[181]. Furthermore, these postsynaptic states could be multiplicatively amplified by state-dependent modulation of plasticity at presynaptic release sites[182].

Concluding remarks

Like synaptic plasticity — and, indeed, memory — the term metaplasticity refers to a variety of processes that layer over each other. Synapse-specific regulation

Memory consolidation
A protein-synthesis-dependent process of memory stabilization occuring over hours in animals and for up to years in humans that renders the memory resistant to change.

Amblyopia
Poor vision, usually occurring in one eye, that is associated with a prolonged period of indistinct visual stimulation or visual system dysfunction during development.

Ischaemic preconditioning
(IPC). A phenomenon observed both clinically and experimentally whereby a mild ischaemic event 'primes' a tissue by activating endogenous cellular protective mechanisms that amelioriate the neurotoxic outcome of a later, more severe ischaemic event.

provides local control, whereas wider heterosynaptic and network changes provide more global regulation. Together, these metaplasticity processes represent a major form of adaptation that helps to keep synaptic efficacy within a dynamic range and larger neural networks in the appropriate state for learning. However, the metaplasticity field is still young, and more extensive studies are required of its molecular mechanisms, their effects on network function and their contributions to learning and memory. Harnessing these regulatory mechanisms might also prove to have important clinical usefulness, particularly as the more tempting direct manipulations of plasticity processes are likely to be fraught with severe side-effects. However, with the multitude of possible mechanisms for study and the excitement which that generates comes the caution that not all plasticity regulation is metaplasticity, and it is important to retain rigor in the design and interpretation of the experiments that address this fascinating and complex topic.

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DATABASES

Entrez Gene: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
brain-derived neurotrophic factor | αCaMKII | elongation factor 1α | elongation factor 2 | ERK1 | ERK2 | mTOR | neurogranin | p38 MAPK | poly-A binding protein 1 | ribosomal protein S6
OMIM: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM
Alzheimer's disease | Down syndrome | Fragile X-linked mental retardation syndrome | Huntington's disease | Parkinson's disease

FURTHER INFORMATION

Wickliffe Abraham's homepage:
http://psy.otago.ac.nz/staff/abraham.html

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