Synaptic plasticity: hippocampal LTP

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One of the most intensively studied forms of synaptic plasticity is long-term potentiation (LTP). The past year has seen further evidence advanced on both sides of the presynaptic/postsynaptic locus of expression debate, without an obvious path to reconcile the two views. Real progress has been made, however, in clarifying the possible role of nitric oxide as a retrograde messenger and the cellular location of its synthetic enzyme. Intriguing glimpses of the complex involvement of metabotropic glutamate receptors in the induction of LTP have also appeared.

Current Opinion in Neurobiology 1995, 5:324–334

Introduction

It is widely believed that plastic changes in the strengths of synaptic connections between neurones are central to the process of information storage in the brain. Many forms of this type of change have been described from various regions of the central nervous system. Our brief was to review recent advances over the past year or so in the study of synaptic plasticity in about 2000 words with 50 references. Such is the continued high level of activity in the field that, by focusing on LTP, by not setting foot outside the hippocampus and by considering only the very end of 1993 and onwards, we have been able to keep the reference list to just over 100. We apologize to those authors whose contributions fell outside our boundaries or, worse still, slipped through the meshes of our net.

Unfortunately, the field is bedevilled by controversy and inconsistency, not only in interpretation but also in the primary data obtained by different laboratories. Here, we review recent publications from the perspective that some of the complexities and controversies may be the result of different experimental approaches, uncovering only one facet of a multi-faceted process.

How can synapses be made stronger?

Broadly defined, LTP is a long-lasting, use-dependent increase in synaptic strength, which has been identified at synapses in several brain areas. It has been perhaps most intensively studied in the hippocampus, a structure that has long been implicated in at least some forms of memory. The main trigger for the induction of LTP appears to be a local increase in the concentration of Ca^{2+} in the postsynaptic neurone. However, the nature of the change that causes the increase in strength of the presynaptic–postsynaptic connection is still far from clear. Following the arrival of an action potential, neurotransmitter is released from the presynaptic terminals of most chemical synapses in the form of discrete, multimolecular packets known as quanta. A particular synaptic connection might involve one or several sites that can release quanta, and it seems that these sites function in a probabilistic manner: that is to say, not every site releases a quantum every time an action potential arrives, but does so with a certain probability, known as the release probability *P*. The neurotransmitter in each packet released then acts on receptors in the postsynaptic cell membrane and produces an electrical response of characteristic size known as the quantal size.

A synaptic connection could thus be made stronger in several ways. These could include increasing the number of release sites involved, their probability of release and the quantal size, or any combination of these. The first two changes would increase the average number of quanta released per action potential, and are conventionally regarded as properties of the presynaptic terminal. Quantal size is thought to be determined primarily by the number and properties of the receptors in the postsynaptic membrane. It is not difficult to think of ways in

Abbreviations

ACPD—1S,3R-aminocyclopentane dicarboxylate; **AMPA**—α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate; **APV**—2-amino-5-phosphonovalerate; **BAPTA**—1,2-bis(o-aminophenoxy)ethane-*N,N,N′,N′*-tetraacetic acid; **CaMKII**—Ca^{2+}/calmodulin-dependent protein kinase II; **EPSC**—excitatory postsynaptic current; **EPSP**—excitatory postsynaptic potential; **GABA**—γ-aminobutyric acid; **LTD**—long-term depression; **LTP**–long-term potentiation; **MCPG**—[RS]-α-methyl-4-carboxyphenylglycine; **mGluR**—metabotropic glutamate receptor; **MK-801**—(+)-5-methyl-10,11-dihydro-5*H*-dibenzo(*a,d*)cyclohepten-5,10-imine; **NMDA**—*N*-methyl-D-aspartate; **NMDAR**—NMDA-type glutamate receptor; **NO**–nitric oxide; **NOS**—NO synthase; ***P***—probability of neurotransmitter release; **PAF**—platelet-activating factor; **PKA**—protein kinase A; **PKC**—protein kinase C; **PPF**—paired-pulse facilitation; **STP**—short-term potentiation.

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which the distinction between presynaptic and postsynaptic factors could be blurred; nevertheless, possible mechanisms of LTP expression are often categorized by the locus within the synapse at which they are likely to operate. As it appears that LTP can be triggered postsynaptically, it seems logical to assume that to mediate an effect on presynaptic factors some form of 'retrograde message' passes back to the presynaptic terminals.

A feature of recent LTP research has been the diversity of experimental results obtained by different laboratories. Central to the problem is the absence of a single, simple answer to the question of the synaptic locus of LTP expression. This uncertainty leaves studies of mechanisms and signalling pathways without a clear goal or target, and we will turn to this issue first.

The locus of expression of LTP: is it presynaptic or postsynaptic?

We can't help wishing that the invitation to write this review had come a year earlier. After a prolonged controversy over the synaptic locus of LTP expression in hippocampal area CA1, the end of 1992 saw publications from three independent laboratories to the effect that expression could involve both presynaptic and postsynaptic changes, to varying degrees, depending on circumstances [1–3]. It was even suggested that it might be possible to predict the locus of the change from the initial setting of the presynaptic release mechanism [2,3]. We [2] found that different synapses, even when recorded under apparently similar conditions, could show widely different release probabilities, a notion that has since received some additional support from work in CA1 [4], although for population rather than single-fibre inputs. Connections mediated by synapses with an initially low *P* showed mainly an increase in *P* with LTP, whereas those that already had a moderate or high *P* showed mainly an increase in quantal size with LTP (Fig. 1). The level of extracellular Ca^{2+} had an influence on *P*, and some of the previous apparently contradictory data could be reconciled on that basis. 1993 was a relatively quiet year, and there seemed to be some danger of an outbreak of peace on the LTP front.

By the end of 1993, we had extended our analysis to include the related phenomenon of short-term potentiation (STP) [5•] — which is similar to LTP in many ways, but lasts between 5 minutes and one hour, depending on who is defining it (!) — and shown that, whether induced by tetanus or using intracellular current injection, the locus depended on the initial release probability of the synapses in exactly the same way as during LTP (Fig. 1). But 1994 has seen the resumption of hostilities (see [6]), with a striking feature being the wide discrepancies in the primary data obtained by different groups, not just in their detailed interpretation.

Manabe and Nicoll [7•] showed that the rate of decline of the NMDA-mediated excitatory postsynaptic current (EPSC) in the presence of MK-801, an irreversible open-channel NMDA receptor antagonist, which should be strongly dependent on the quantal release probability, was apparently unaffected by the induction of LTP. This suggests that LTP is not expressed by an increase in the probability of neurotransmitter release. However, Stevens and Wang [8•] reported that when single fibre inputs to CA1 pyramidal cells displayed LTP, the proportion of transmission failures decreased, but the non-failure responses stayed the same size. This result is most easily explained if the inputs were mediated by a single release site that showed an increase in release probability. An alternative explanation, that the excitability of the afferent fibre had been increased [9•], is rendered less likely by the Stevens group's [8•] use of a relatively high temperature (31.5°C), because the changes in fibre excitability are reported to be minimal above 32°C.

Paired-pulse facilitation

In a number of earlier studies, there had been something unusually close to agreement that the induction of LTP does not affect the degree of paired-pulse facilitation (PPF). PPF is generally taken to be an indicator of presynaptic release probability, so this is consistent with LTP expression not involving changes in *P*. Recently, however, three studies have demonstrated changes in PPF following LTP induction in the dentate gyrus [10•] and in CA1 [11,12•]. In each case, those connections showing the largest degree of PPF initially showed the greatest reduction in PPF with LTP, in line with the idea that synapses with a low initial *P* are most likely to show an increase in *P* with LTP. In two of these studies [10•,12•], connections initially showing little PPF could actually show an increase in PPF with LTP. Schulz *et al.* [12•] suggest that this could be due to the recruitment of additional release sites that have a low release probability. An alternative might be that the large responses recorded in these studies would involve release sites with a wide range of *P* values, and not all sites might contribute equally to LTP. If sites with low or moderate *P* values showed a greater overall enhancement (perhaps by showing both presynaptic and postsynaptic increases, whereas high *P* sites showed only postsynaptic changes), then the level of PPF of the whole population of synapses could increase. An interesting cautionary tale for the use of PPF as a measure of *P* is given by Clark *et al.* [13], who found that PPF of NMDA receptor mediated EPSCs was strongly dependent on postsynaptic voltage, suggesting the involvement of postsynaptic factors.

The dual NMDA/AMPA components of EPSCs

Evidence in favour of a postsynaptic locus for LTP came from the demonstration that increases in postsynaptic Ca^{2+} can induce an increase in the size of miniature EPSCs and responses to applications of AMPA [14].

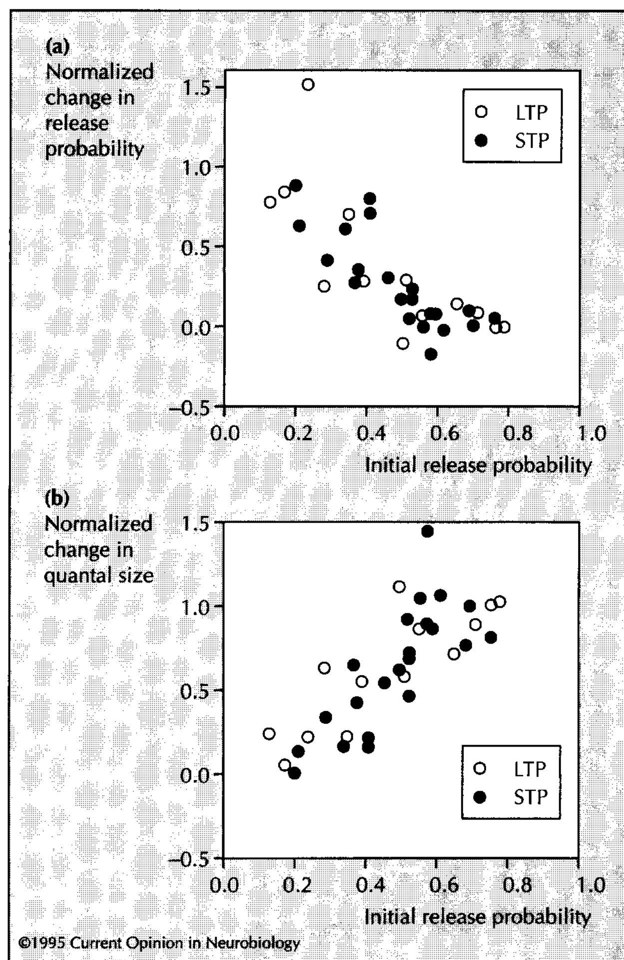

Fig. 1. The relation of the locus of expression of both LTP and STP to the initial release probability of the synapse. Abscissae show release probability for individual synaptic connections, evoked by minimal stimulation, estimated just before the induction of potentiation. Ordinates show the normalized change in **(a)** release probability (presynaptic) and **(b)** quantal size (postsynaptic) soon after induction of LTP (open circles) and STP (filled circles). Zero indicates no change. Before induction, connections vary widely in release probability, ranging from 0.1 to 0.8. Synapses with low initial probability show mainly an increase in probability, whereas high release probability synapses show predominantly an increase in quantal size. Note that this analysis procedure ascribes any potentiation not due to a change in quantal size to a change in release probability. Modified from [5•].

Most excitatory synapses in CA1 seem to have both the NMDA and AMPA types of glutamate receptors, so the EPSC usually contains contributions from both. Kullmann [15•] reported that LTP induction caused changes in the size and variability of the AMPA receptor component, but no change in the size or variability of the contribution from the NMDA receptors. On the other hand, Clark and Collingridge [16••] reported equal potentiation of the two components during both LTP and STP, consistent with a presynaptic locus. This form of LTP could be induced by tetanic stimulation even after prolonged whole-cell recording, which has been reported to prevent LTP induction, presumably by washout of essential components from the postsynaptic neurone. Lynch *et al.* [17] showed an increase in the levels of the synaptic vesicle proteins synapsin, synaptotagmin and synaptophysin three hours after LTP induction, indicative of an increase in neurotransmitter release, at least in the later stages of expression. Later still, 48 hours after induction, a change in NMDA receptor expression in postsynaptic cells has been reported [18].

In line with previous reports from their laboratory, Asztely *et al.* [19•] also reported increases of both the AMPA and NMDA receptor components during LTP, with the AMPA component elevated more; this is consistent with a mixed presynaptic and postsynaptic action. They found no evidence of changes in the time course of LTP or relative NMDA/AMPA contributions when they altered initial release probabilities using adenosine or its antagonists. In their experiments, a large number of input fibres was stimulated, so it is not possible to know how the presynaptic and postsynaptic effects were distributed between the fibres. For similar reasons, it is unclear how well they tested the idea of different loci for single fibres with different average probability of release when applying adenosine or its antagonists. Although adenosine does tend to reduce, on average, the release probability, it is not known what the distribution and the strength of the effect is on different fibres; adenosine also tends to inhibit the generation of LTP [20]. The correlation between the locus of expression and the initial release probability reported by Larkman *et al.* [2] and Liao *et al.* [3] would only be expected if similar induction conditions were used in the different experiments. In the Asztely *et al.* [19•] experiments, the number of afferent fibres stimulated was adjusted after the release probability has been altered by adenosine. Interestingly, adenosine may be released following tetanic stimulation, probably from interneurones, and mediates a widespread heterosynaptic depression [21].

Unlikely mechanisms

Although there is nothing resembling a consensus view of the mechanism and locus of LTP expression, there has perhaps been some progress towards eliminating some possible mechanisms. A number of recent quantal analysis studies have reported very low levels of quantal variance at excitatory synapses in CA1, and one suggested explanation for this is that the receptors associated with a release site are essentially saturated by the release of a single quantum of neurotransmitter ([3,22–26]; but see [27]). This suggestion has received experimental support from studies with cultured neurones using two very different approaches [28,29] and also for inhibitory synapses in the dentate gyrus [30]. This makes it unlikely that large changes in quantal size could be achieved by loading more neurotransmitter into each synaptic vesicle, or by releasing multiple vesicles simultaneously at a given site. Thus, the conventional view that quantal size is determined postsynaptically lives to fight for another day at least. Another possible presynaptic mechanism may have

to go to the back of the queue with the demonstration that presynaptic action potentials are not broadened [31] and presynaptic Ca^{2+} entry is not increased [32•] following LTP induction. However, in these studies it is not known whether the locus of the LTP that has been produced is presynaptic.

NMDA receptors

It is widely agreed that LTP induction in CA1 involves a rise in the Ca^{2+} concentration of the postsynaptic cell, due to entry mediated largely, but not necessarily exclusively [14,33], by the NMDA-type glutamate receptors (NMDARs). Recent gene knockout experiments have confirmed the central importance of this receptor. Mice lacking the NMDAR1 subunit show serious deficits and generally die within a day of birth [34]. Mice lacking NMDAR2A subunit survive and develop quite normally, but show reduced NMDA synaptic currents. They also show significantly reduced, although not abolished, LTP and impaired performance in the Morris water maze [35].

Mossy-fibre input

LTP at the mossy-fibre to CA3 synapse can be independent of NMDA receptor activation and presents different, but no less awkward, challenges. Here the locus of expression is less of a problem, but the mechanism of induction is highly controversial. It seems a good bet that expression is predominantly presynaptic, based on an interaction with PPF [36,37], at least at early times [38], and on quantal analysis [37].

It has been suggested that the induction of LTP at mossy-fibre synapses is presynaptic and non-associative [36], but there is considerable evidence inconsistent with this (see [39]). Several factors contribute to the uncertainty, including the technical difficulty of obtaining uncontaminated mossy-fibre inputs and the involvement of a range of modulatory factors [39], such as opioid peptides, which are probably released from the mossy-fibre terminals themselves in a frequency-dependent manner [40,41]. Recently, it has been reported [42] that the number of mossy fibres stimulated is important, implying a degree of cooperativity. Low intensity trains that were normally ineffective could induce LTP if paired with commissural stimulation, and even single mossy-fibre pulses could show LTP if paired with commissural trains in the presence of a μ-opioid receptor agonist, suggesting an associative process, probably involving the postsynaptic neurone [42]. A further complication arises from the demonstration that mutant mice lacking the mGluR1 subtype of metabotropic glutamate receptors show greatly impaired LTP in mossy fibres, although it is not affected in the dentate gyrus or in CA1 [43]. Finally, blockade of either N- or P-type Ca^{2+} channels, each of which causes a dramatic reduction in mossy fibre synaptic transmission, does not reduce the ability of the surviving transmission to show LTP [44].

Retrograde messengers

Nowhere is the need for a resolution of the presynaptic versus postsynaptic controversy more urgent than in retrograde messenger research. It goes without saying that if LTP is expressed postsynaptically, blockade of the synthesis or action of candidate retrograde messenger molecules will be without effect. If LTP can be expressed either presynaptically or postsynaptically — possibly by a variety of mechanisms depending on the precise circumstances — it is only to be expected that major differences in the findings of different laboratories will result.

Thus, the past year has brought the by now familiar litany of claims that nitric oxide (NO) does or does not play a role in LTP (see [45]). Infusion of an NO donor into the CA1 region of conscious rats produced a rise in the extracellular levels of glutamate and GABA [46]. Other groups, however, have been unable to demonstrate any substantial role under particular conditions [47–49]. A pleasing trend has been for close attention to be paid to experimental details. It has been reported that the age of the animal and the experimental temperature are important factors [50], but also the intensity and pattern of the stimulation can influence whether NO induces potentiation or depression [51,52•].

An ongoing problem with the notion of NO as a retrograde messenger has been the difficulty of demonstrating the existence of NO synthase (NOS) in the somata and dendrites of pyramidal cells in the CA1 region (see [53] for review). This year has seen some real progress on this front, with the use of improved fixation procedures to reveal diaphorase activity [54], as well as immunocytochemistry and *in situ* hybridization to demonstrate the presence of NOS in these structures [55]. Further clarification came with the finding that it may be the so-called 'endothelial', as opposed to the 'neuronal', form of NOS that is the principal source of NO in CA1 pyramidal cells [54,56••].

The preservation of synaptic specificity for potentiation mediated by any freely diffusible retrograde messengers has always been of concern, and was elegantly highlighted for NO last year. Examining the role of NO in LTP, Schuman and Madison [57••] presented compelling evidence that induction of LTP (by pairing synaptic activation with depolarization of the postsynaptic cell by current injection) in one CA1 cell can cause LTP in neighbouring cells that did not undergo pairing. Therefore, this form of LTP, which is prevented by blockade of NOS in the paired cell, does not conform to 'Hebbian' principles.

The case for a rival retrograde messenger candidate, arachidonic acid, has also been developed further with the demonstration that the synergism between arachi-

donic acid and mGluR activation previously demonstrated in neocortex [58,59] also operates in the hippocampus [60]. The synergism is thought to depend on the activation of protein kinase C (PKC) and leads to enhanced glutamate release. Rapid desensitization of the presynaptic glutamate receptor may help to prevent excessive activation and possible neurotoxicity resulting from the positive feedback loop [61]. In aged rats, there is a reduction in membrane arachidonic acid concentration that is correlated with the loss of the ability to sustain LTP [62]. A further complication to the arachidonic acid story has emerged with the finding that it depresses the action of non-NMDA receptors [63] but potentiates NMDA receptors [64].

Platelet-activating factor (PAF) also received further support as a retrograde messenger candidate: applied PAF and mild presynaptic stimulation cause LTP; PAF antagonists prevent LTP, but spare STP; and tetanus-induced LTP occludes PAF-mediated potentiation [65•]. However, PAF-mediated potentiation only partially occludes tetanus-induced LTP, leading Kato *et al.* [65•] to suggest, refreshingly, that other mechanisms might also contribute. Carbon monoxide has had a restful year.

A speculative footnote to the consideration of possible retrograde messenger mechanisms comes from the observation that both ionotropic and metabotropic glutamate receptors have extraordinarily large extracellular domains, that appear excessive for the task of binding to the small ligand glutamate. These domains could extend a significant distance across the synaptic cleft and could serve some additional function, perhaps that of passing retrograde signals to the presynaptic terminal [66].

Metabotropic glutamate receptors

Over recent years, increasing attention has been focused on the role played by mGluRs in synaptic plasticity [67]. Several earlier studies suggested that metabotropic activation can facilitate the induction of LTP. As more specific and potent antagonists and agonists have become available [68], one might have expected that the picture would have become clearer.

Collingridge and colleagues [69] showed that application of the metabotropic agonist ACPD induced a slow-onset, long-lasting potentiation of field EPSPs in CA1. The metabotropic antagonist MCPG not only blocked this effect, but also prevented the induction of LTP by conventional tetanus protocols, although STP could still occur [69]. This is consistent with the idea that metabotropic activation could provide the additional trigger necessary for the conversion of STP to LTP, possibly involving the augmentation of the activation of NMDA receptors [69] or by stimulation of inositol lipid turnover and release of Ca^{2+} from intracellular stores [70]. Application of metabotropic agonists induces a long-lasting enhancement of pharmacologically isolated NMDA EPSCs in dentate granule cells [71]. This effect is virtually abolished by MCPG and is occluded by prior tetanus-induced LTP.

In a fascinating series of experiments, Collingridge's group [72••] went on to show that mGluRs could activate some form of 'switch' that could remain set for hours and remove the need for mGluR activation during subsequent induction of LTP. This switch can be reset by low-frequency stimulation, a process that itself involves mGluR activation. However, in the LTP field, each apparent step forward is often accompanied by one or more steps back. Chinestra *et al.* [73] reported that MCPG neither antagonized the action of ACPD nor prevented the induction of LTP. In the hands of Manzoni *et al.* [74], MCPG antagonized mGluR but did not prevent LTP. Recently, Chinestra *et al.* [75] have reported that ACPD can produce slow-onset potentiation in a minority of slices, but they suggest that this is entirely different from more conventional forms of LTP. This form of potentiation appears to involve the recruitment of additional afferent fibres by the lowering of action potential thresholds, either by a persistent block of K^+ channels, or by an elevation of extracellular K^+ caused by paroxysmal firing of CA3 cells, as the effect is abolished by the removal of the CA3 region from the slice. However, recent work from the Collingridge group (GL Collingridge, personal communication) shows that ACPD can produce long-lasting potentiation without epileptiform activity in CA3 or any change in the presynaptic fibre volley. Differences in experimental conditions, such as species, temperature and even the design of the slice chamber have been advanced as possible contributors to the discrepancies [74,75]. In addition, it has been reported that the role of mGluRs in LTP changes during development [76].

Relations between LTP, STP and LTD

A theme to have emerged in recent years is to view LTP as one of a family of related changes in synaptic efficacy, which include STP and LTD (see [77,78]). STP is NMDA receptor dependent and can be occluded by LTP [79]. However, STP is often spared by blockade of protein kinase activity that prevents LTP. Recently, it has been shown that the kinase inhibitor staurosporine, at a concentration at which it primarily blocks PKC, inhibits STP in the dentate gyrus to the same extent as LTP [80•]. This supports the notion that STP and LTP share common mechanisms and may represent parts of a spectrum of changes of variable duration [81]. Quantal analysis during STP induced by either pairing or tetanus procedures is consistent with this. Not only can STP involve both presynaptic and postsynaptic changes, but the relative contribution of each depends on the initial release probability in the same way as for LTP ([5•]; see Fig. 1). A note of caution must be sounded, however, given the finding that STP, but not LTP, can be induced in apical

dendrites loaded with the Ca^{2+} chelator BAPTA [82]. A possible explanation might be that the concentration of the chelator at the synaptic site was not sufficient to prevent a modest rise in intracellular free Ca^{2+}.

Insight into the possible role of STP in learning has come recently from an unlikely source. In the course of research into prion diseases such as scrapie, mutant mice lacking a functional gene for prion protein were produced [83]. These mice behaved surprisingly normally, and showed no learning impairment when tested in the Morris water maze [83]. It has now been shown that hippocampal slices from these mice show only STP rather than LTP in response to tetanic stimulation [84]. It may be that sustained LTP is not necessary for this task.

Long-term depression (LTD) can also exist in a variety of forms, at least some of which share features with LTP and STP (see [85,86]). Properties in common with LTP include input specificity, a requirement for NMDA receptor activation and a rise in postsynaptic Ca^{2+} [86], as well as a lack of reproducibility between research groups (e.g. [87])! Studies published during the past year have reported that prolonged 1–2 Hz stimulation can induce a robust, APV-sensitive LTD in slices from 12–18 day old rats at 30°C [88•] and in 16–20 day old rats at room temperature [89]. Similar treatment did not induce LTD in adult rats *in vivo* [90] or in slices from 28–42 day old rats at 30°C [91]. In the latter case, this treatment could cause depotentiation of previously potentiated synapses, and this depotentiation was reduced by metabotropic receptor blockade with MCPG, but was not sensitive to APV. In 3–7 day old rats at 21–23°C, stimulation at 5 Hz for 3 minutes induced LTD that was not sensitive to APV but was prevented by MCPG [92]. Tetanic stimulation of mossy fibre to CA3 synapses produced LTD in 6–14 day old rats but LTP in 15–24 day old animals [93]. Such a diversity of experimental procedures and resultant phenomena should ensure that the unravelling of LTD mechanisms proceeds about as smoothly and amicably as for LTP.

Protein phosphorylation/dephosphorylation

Most researchers would agree that in all members of the family of synaptic efficacy changes outlined above, changes in intracellular free Ca^{2+} and in the levels of protein phosphorylation play pivotal roles. Unfortunately, the same could be said for a great many cellular processes. Many different pathways have been implicated in the various processes under different conditions, although it seems that, generally, potentiations involve increased levels of phosphorylation by enhanced kinase activity and depressions involve reductions in phosphorylation (but see [82]).

Ca^{2+}/calmodulin-dependent kinase II (CaMKII) has long been proposed as a major player during LTP, and further compelling evidence in its favour has been presented over the past year. An innovative approach was the use of vaccinia virus infection to introduce a constitutively active form of the enzyme into cells in hippocampal slices [94••]. This approach allows the mouse to develop with the kinase operating normally, in contrast to the gene knockout approach. For example, knockout of Fyn tyrosine kinase may impair hippocampal development [95,96] and myelination [97], as well as affecting LTP specifically. Virus-infected slices showed enhanced excitatory transmission, and conventional LTP-inducing procedures induced no further long-lasting potentiation. The authors interpretation of these results is that the elevated CaMKII activity in postsynaptic cells triggered LTP maximally, and so prevented any further potentiation. Blockade of CaMKII is known to prevent LTP (although some of the blocking agents used may not be as specific as was hoped [98]), and mutant mice lacking αCaMKII show impaired LTP [99,100], and impaired STP and LTD as well [101]. CaMKII blockade also prevents the transient enhancement produced by the entry of Ca^{2+} into postsynaptic cells through voltage-gated Ca^{2+} channels [102]. The location and abundance of CaMKII in postsynaptic densities has always made it a promising candidate, and recent studies of its subunit structure and autophosphorylation properties suggest that it is well suited to show a prolonged enhancement of activity following sequential Ca^{2+} transients [103]. Pettit *et al.* [94••] conclude that postsynaptic CaMKII activity is both necessary and sufficient to generate LTP. It is possible that this conclusion only applies to the postsynaptic form of LTP.

There is, of course, ample evidence for the involvement of other signalling pathways, and the past year has seen evidence, often from studies on transgenic mice, advanced for PKC [104–107], guanylyl cyclase [108], adenylyl cyclase [109], protein kinase A (PKA) [38,110], cAMP-responsive element-binding protein (see [111]), neural cell adhesion molecules [112] and, for later phases, transcription [113]. *In situ* hybridization studies reveal an increase in the expression of αCaMKII and γPKC at 2 hours after LTP induction, and of ERK2 and raf-B by 24 hours [114].

Inhibition of protein phosphatases (see [115]) by calyculin A allows treatments that would normally induce LTD (prolonged 1 Hz stimulation) or only transient potentiation (depolarizing pulses in the absence of synaptic stimulation) to produce long-lasting enhancements, apparently by predominantly presynaptic mechanisms in the former case [116] and postsynaptic in the latter [102]. Blockade of phosphatase 2B (calcineurin) is reported to prevent LTP in adult rats at 30–32°C [82], but to have no effect on LTP in 12–20 day old rats at room temperature while blocking LTD [117••]. Calyculin A is reported to have no effect on basal synaptic transmission in 3–5 week old guinea pigs at 20–25°C [102], but to induce a long-lasting enhancement in adult rats [118], possibly by blockade of presynaptic Ca^{2+}-activated K^+ channels leading to enhanced neurotransmitter release.

Conclusions

We can only conclude, in agreement with Mulkey *et al.* [117••], that the control of synaptic efficacy is regulated by a complicated network of interacting signalling cascades. Which cascade dominates at any given instance may depend, in part, on the spatial and temporal dynamics of changes in postsynaptic Ca^{2+} concentration. The list of procedures that can induce LTP is a long one, which can now be extended to include 'intracellular tetanization' [119] and electroconvulsive therapy [120], as well as the more familiar tetanus and pairing protocols.

While LTP was regarded as a unitary phenomenon, the means used to produce it could be regarded as irrelevant, so long as an end result was achieved. As we become aware of the diversity of pathways and related changes that can be called into play under different circumstances, the details of the experimental conditions become vitally important. Thus, pairing low-frequency stimulation with depolarization of the postsynaptic cell might, for example, produce less mGluR activation than tetanic stimulation procedures and induce a different variant of LTP. Even under similar conditions, we should not expect all synapses to behave equally. To take an example from our own corner of the field, if different connections have different release probabilities, they will show different apparent thresholds for the induction of the various types of change. A 50 Hz train of stimuli might be seen by a postsynaptic cell as a 25 Hz delivery of neurotransmitter quanta at a high *P* synapse, but as only a 2 Hz delivery at one with low *P* on the same cell. If large stimuli, activating many fibres are used, the observed result will represent the summed response of many synapses showing changes of differing magnitude, duration and possibly sign (i.e. potentiation or depression), mediated by different signalling pathways. The use of extracellular field potential recording confers long-term recording stability, helpful for pharmacological studies, but may obscure the real complexity of the underlying processes. Future progress may be expedited by paying close attention to both the experimental conditions and procedures and also to the status of the individual synapses concerned.

Perhaps we should not be surprised that different procedures have led to different results; what seems truly baffling is the way in which individual research groups have been able to perform experiments that consistently reveal only limited parts of the total network of pathways and outcomes that is apparent from the literature as a whole.

Acknowledgements

The authors' research is supported by the Wellcome Trust and the Royal Society.

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- • of special interest
- •• of outstanding interest

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Using similar quantal analysis techniques to the earlier paper [2], it is reported that STP, like LTP, can involve changes in both quantal size and the number of quanta released. The relative contribution of these two processes is related to the initial release probability of the synapses, in the same way as for LTP.

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During repetitive stimulation in the presence of the irreversible open-channel NMDA blocker MK-801, the NMDA receptor component of the EPSC declines at a rate that depends on the probability of neurotransmitter release. This rate is not altered following induction of LTP by pairing, suggesting that LTP, in this case, does not involve a change in release probability.

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