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COMMENTARY

LTP and Spatial Learning—Where to Next?

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ABSTRACT Hebb suggested, in 1949, that memories could be stored by forming associative connections between neurons if the criterion for increasing the connection strength between them be that they were active simultaneously. Much attention has been devoted towards trying to determine a) if there is a physiological substrate of such a rule, and b) if so, whether the phenomenon participates in real-life memory formation. The discovery of the electrically induced increase in synaptic strength known as long-term potentiation (LTP), in the early 1970s, demonstrated that a neural version of the Hebb rule could be observed under laboratory conditions in the hippocampus, a structure important for some types of learning. However, a quarter of a century later, the evidence linking LTP to learning and memory is still contradictory. The purpose of the present article is to review and assess the types of approach that have been taken in trying to determine whether hippocampal synaptic plasticity participates in memory formation. *Hippocampus 7:95–110, 1997.*

KEY WORDS: long-term potentiation; synaptic plasticity; hippocampus; spatial learning

INTRODUCTION

The nature of the physiological basis of learning and memory remains an elusive problem in neurobiology. The current most popular hypothesis, that memories might be stored by changing the strength of inter-neuronal connections, was proposed at the turn of the century by Ramón y Cajal (1911) and later formalised by Hebb (1949). The hypothesis was unable to be directly tested, however, because single synapses could not then (and still cannot) be isolated in behaving (i.e., learning) animals. However, in the early 1970s, Bliss and his colleagues advanced an experimental model of synaptic plasticity, long-term potentiation (LTP), which appeared to circumvent many of the problems involved with recording single synapses (Bliss and Lømo, 1973; Bliss and Gardner-Medwin, 1973). Long-term potentiation consisted of an electrically induced increase in synaptic strength triggered in large numbers of fibres simultaneously, resulting in a combined increase of synaptic strength so large as to be easily measured by extracellular electrodes, even in awake and mobile animals. It was observed in the hippocampus, a structure known to be important for some types of memory formation, and found to last for many days or weeks. It was suggested that LTP might represent a synchronous, artificially induced form of the type of synaptic plasticity that putatively occurs naturally, in a much smaller proportion of synapses, during learning.

The method of LTP induction appeared to offer a way in which synaptic events could be magnified, so as to be observable even during the unstable recording situations that occur during learning. As a result, over the intervening 25 years the cellular basis of LTP has been extensively researched and is now relatively well understood. In parallel with the molecular research, a considerable number of behavioral studies have been carried out, with the aim of determining whether LTP really does engage the learning machinery. The most thoroughly studied structure has been the dentate gyrus, whose integrity is essential for normal spatial learning to occur and whose synapses are relatively easy to stimulate and record in freely moving animals. It is the purpose of this article to review the behavioral literature to assess a) whether the data support the hypothesis that an LTP-like mechanism underlies the spatial learning function of the dentate gyrus, and b) whether such an approach could, in principle, prove or disprove the hypothesis.

LTP

In the behaving rat, LTP is most easily observed in the perforant path connection between the entorhinal cortex (EC) and hippocampal dentate gyrus (DG). A comprehensive analysis of the components of population granule cell responses to perforant path stimulation may be found in Lømo (1971a). The medial and lateral components of the perforant path between them project to the entire septo-temporal extent of the dentate gyrus, making excitatory synaptic connections in the molecular layer. The fibres also make excitatory contact with basket cells connecting to dentate granule cells, producing a feed-forward inhibitory influence on the granule cell response. In addition, the granule cells themselves contact basket cells, producing feed-back inhibition. A stimulating electrode placed in the angular bundle of the perforant path therefore exerts a monosynaptic excitatory effect and a di- and tri-synaptic inhibitory effect on the target granule cells (as well as effects on CA3 and CA1 cells). Stimulation of this pathway with a single

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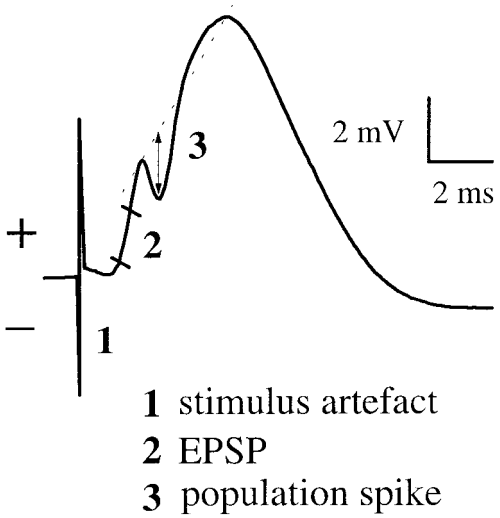

FIGURE 1. Evoked response of a population of dentate granule cells following an electrical stimulus to the perforant path, showing the two parameters (EPSP slope and population spike height, 2 and 3 respectively) that are used to describe the size of the waveform. 1) Stimulus artefact produced by the current pulse, followed by a short delay representing axonal and synaptic transmission of the stimulus. 2) Rising phase of the EPSP. The two short lines represent the cursors between which the EPSP slope is calculated by linear regression. 3) Downgoing notch of the population spike. The length of the arrowed line from the tip of the spike to the dotted line drawn between the two local maxima represents the population spike height.

electrical shock results in synchronous activation of dentate granule cells, causing an excitatory post-synaptic potential (EPSP), and sometimes cell firing (resulting in a population spike: Fig. 1).

Bliss and colleagues discovered that if the single test pulses are temporarily replaced by a train of high-frequency (100–400 Hz) pulses (Fig. 2B), both the synaptic and somatic components of the response evoked by the test pulses increase (Fig. 2C) and stay increased for hours, and sometimes days or weeks (Bliss and Lømo, 1973; Bliss and Gardner-Medwin, 1973; Barnes, 1979; Racine et al., 1983; Jeffery et al., 1990). After some debate this phenomenon came to be termed long-term potentiation (LTP).

LTP has attracted a great deal of attention because some of its properties are suggestive of those that should be possessed, in theory, by a memory mechanism (e.g., Hebb, 1949). In addition to its long-lasting nature, the properties which make it computationally interesting are associativity, cooperativity and input-specificity (Bliss and Collingridge, 1993). Associativity means that LTP induction in a given synapse may be regulated by other convergent inputs terminating on spatially distant regions of the postsynaptic cells, so that the relevant synapse may not even need to have been tetanized in order to become potentiated (Wigström et al., 1986). Cooperativity is a closely related concept, and refers to the fact that a greater stimulus intensity during tetanization will produce greater LTP because the larger number of stimulated fibres interact to produce a mutual facilitation of LTP induction (McNaughton et al., 1978). Specificity refers to the finding that changes in strength only take place at synapses that had been active (i.e., releasing neurotransmitter) at the time that the LTP-inducing event took place, or within a short time (up to 200 ms) on either side of it. Other synapses contacting the same postsynaptic cell will not become potentiated if they were not active at the time (Andersen et al., 1977; McNaughton and Barnes, 1977; but see Bonhoeffer et al., 1990). These properties all derive from an underlying induction requirement, which is that for LTP to occur the postsynaptic cell must be strongly depolarised at the same time as the presynaptic terminals are releasing neurotransmitter. It is now known that in most regions of the hippocampus (though not all: see Harris and Cotman, 1986; Grover and Teyler, 1990 and Bramham et al., 1991 for exceptions) these induction properties can largely be attributed to a specialised postsynaptic receptor, the NMDA receptor.

The NMDA receptor is unusual because its associated ion channel will only open when the postsynaptic membrane on which it resides is depolarised past a certain threshold, and at the same time neurotransmitter (probably L-glutamate) is released into the synaptic cleft (see Bekkers and Stevens, 1990). Both of these conditions are satisifed during the massive synchronous activation and postsynaptic depolarisation that occurs during a tetanus, but it appears that any method of achieving the two conditions will suffice to trigger LTP induction. For example, LTP will also occur if the postsynaptic cell is artificially depolarised, and this depolarisation is paired with single pulses to afferent fibres (Wigström et al., 1986; Gustafsson and Wigström, 1986; Wigström and Gustafsson, 1985). Conversely, hyperpolarization of the postsynaptic cell blocks LTP induction even when all the other usual requirements are met (Malinow and Miller, 1986). It is this "coincidence detection" characteristic of the NMDA receptor, combined with the longevity of LTP, that has excited speculation that it may be the cellular substrate of the Hebb rule (Wigström and Gustaffson, 1985; Cotman and Monaghan, 1988).

There has been much debate over whether the factors needed to trigger LTP ever occur naturally. It is now generally accepted that LTP can be elicited following patterns of afferent activity resembling those that can occur in neurons. For example, Buszáki et al. (1987) found that pairing single pulses with pharmacologically induced bursts of cellular activity ("sharp waves") could induce LTP. A subthreshold burst of pulses or a single stimulus (known as priming stimulation) followed by a short train of 2–10 pulses induces robust LTP if the priming stimulation precedes the train by an interval of 150–200 ms (Larson et al., 1986; Diamond et al., 1988; Greenstein et al., 1988). This suggests that the temporal patterning of stimulation and not just its strength is important for inducing LTP. The 150 ms interval corresponds to the frequency of endogenous rhythmic hippocampal activity (theta), suggesting that there may be a link between theta and naturally occurring LTP.

Testing the Plasticity/Learning Hypothesis

The postulated chain of events underlying the establishment of a memory trace in a neural circuit is as follows:

Experience → synaptic strength changes (natural plasticity)
→ learning and memory

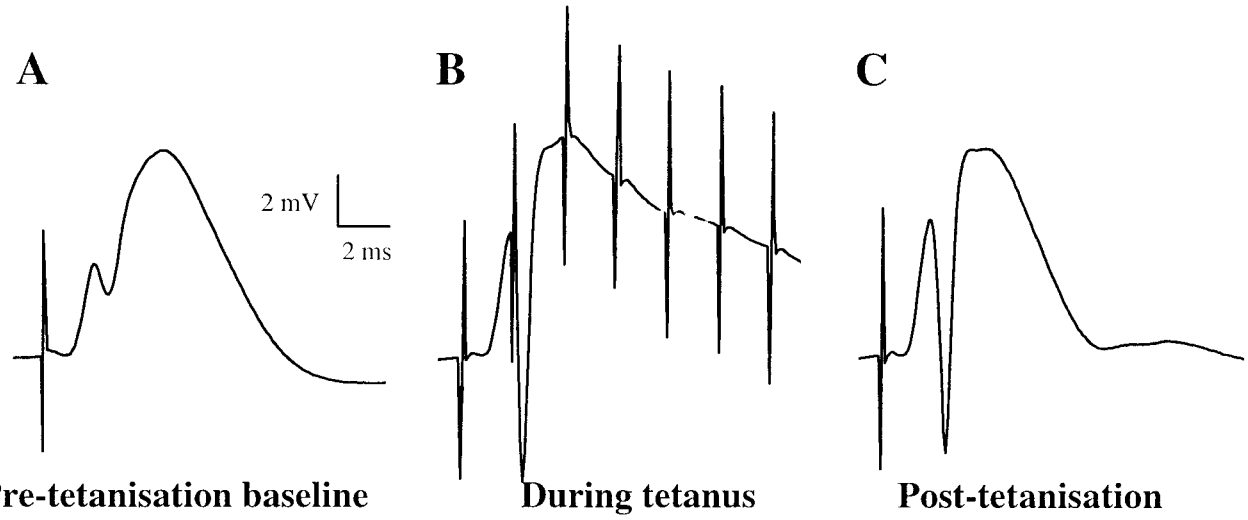

FIGURE 2. Effect of a train of high-frequency electrical stimuli on the size and shape of dentate gyrus evoked potentials. A: A baseline response when stimulus intensity is adjusted so as to evoke a small population spike. B: The shape of the waveform during a 400 Hz tetanus. C: Evoked response to the same intensity stimulus as in A, measured 30 min after tetanization. Both the slope of the EPSP and the height of the population spike are increased, reflecting the greater synaptic efficacy which comprises long-term potentiation.

In LTP induction the usual corresponding chain of events is:

Tetanization → synaptic strength changes (LTP)
→ increased evoked field potential

If the hypothesis is correct that both LTP and learning make use of the same underlying cellular mechanisms, then experimental manipulations of individual links in the either of the two chains might produce corresponding changes in both outcomes: for example, tetanization might affect learning and memory, or a learning experience might affect the subsequent size of the evoked field potential, and so on. This logic underlies nearly all of the experiments that have been conducted to date investigating whether an LTP-like process underlies memory formation. The various types of experiment can be classified as follows: 1) Effect of experience on synaptic strength; 2) Effect of experience on LTP; 3) Effect of LTP induction on learning; 4) Effect of manipulating LTP-type plasticity on learning; 5) Correlation between evoked potential change and learning; 6) Conflation of learning experience with tetanization.

These classes of experiment will be reviewed in turn.

Effect of experience on synaptic strength

The synaptic-plasticity/learning hypothesis postulates that synaptic strengths increase following a learning experience, in which case enhancement of the evoked field response might also be expected (assuming enough synapses participated in the memory formation). This prediction has been tested several times. Sharp et al. (1985) kept five rats in a restricted environment for several weeks, to allow synaptic strengths to decay to their lowest possible levels. They then exposed three of the rats to a rich and spatially complex environment and observed an increase in the size of the population spike with a smaller increase in two animals in the size of the EPSP (the EPSP in the third animal declined). A subsequent study showed that this spike enhancement decayed more quickly in old animals (Sharp et al., 1987), with time constants for young vs. old animals similar to those observed following electrically induced LTP (Barnes, 1979). However the phenomenon differed from LTP in that there was little (first study) or no (second study) change in the size of the EPSP.

Subsequent experiments complicated the picture further. It had previously been observed that over the 5 min after a rat was first placed in a recording chamber (which could be considered a novel environment) the size of the EPSP increased slowly (Barnes, 1979). This phenomenon was examined in more detail by Sharp et al. (1989) who transferred rats between several different environments while recording the evoked responses. While brief handling in the home cage produced very small increases in the EPSP, removal from the home cage and placement in a recording chamber produced substantial EPSP increases (around 30%) developing over 15 min and lasting up to an hour after replacement in the home cage. However, the population spike showed a decrease. The amounts of EPSP increase and spike decrease correlated highly with a quantitative measure of prior exploration. Green et al. (1990) showed that treadmill running of the rats was associated not with a rise but rather with an abrupt fall in the size of the EPSP, a result that appeared to indicate that motor activity alone could not explain the exploration-associated changes. Finally, Croll et al. (1992) showed that, like LTP, exploration-evoked changes were abolished with the NMDA receptor antagonist MK-801.

Again, these evoked response changes did not completely support the hypothesis that LTP was being expressed by these synapses in response to a learning experience, for several reasons. First, the EPSP and population spike appeared to vary inversely.

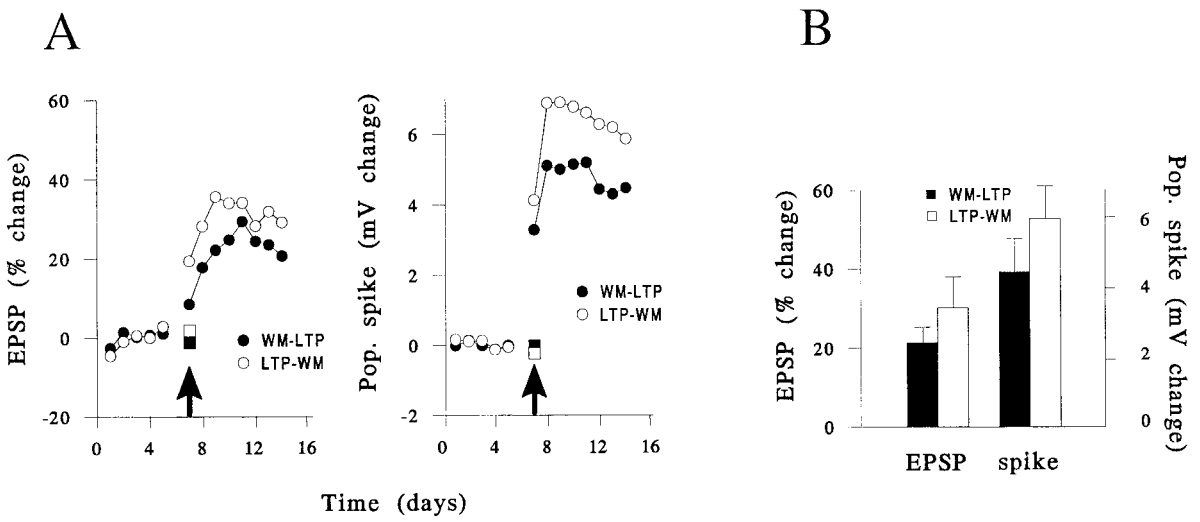

FIGURE 3. The effect of watermaze training on evoked potential size and LTP. A: Size of the responses compared to baseline for the EPSP (left graph) and population spike (right graph). Baseline responses were collected for 5 days. On day 6, WM-LTP rats underwent spatial training in the watermaze while the LTP-WM rats underwent non-spatial pretraining only. On day 7 (arrows), baseline responses were collected and then rats received the first of an 8-day course of tetanization. The pre-tetanization baseline responses did not differ between trained and untrained groups (squares), nor did the amount of LTP achieved after tetanization. B: Total amount of LTP gained after LTP induction to asymptote. Spatially trained rats gained slightly less LTP, but this was not significant.

Second, abrupt decreases of the EPSP were provoked by certain manipulations such as the treadmill-running condition, a behavior that would not be expected of a memory-storing phenomenon. Third, although short-lasting exploration-associated changes were evoked when an animal was placed in a new environment, subsequently placing it in a second new environment failed to produce any further changes, even though new information was presumably being stored. This rapid saturation also would not be expected of a memory mechanism, and differs from LTP, which saturates only slowly and after repeated induction.

The likely explanation for these contradictory findings has been advanced by Moser et al. (1993b). Puzzled by observations that spatial watermaze learning was accompanied by substantial *decreases* in EPSP size, these authors conducted a careful study of brain temperature during different behavioral activities and found unexpected and large changes in temperature following apparently trivial physical exercise. An increase in hippocampal temperature was very highly correlated with an increase in EPSP slope and a decrease in population spike height—exactly the changes associated in the above studies with exploration. Treadmill running in rats acclimatised to the new environment produced large increases in both brain temperature and EPSP size. However, when non-habituated rats were used the EPSP showed an abrupt fall, as in the Green et al. (1990) study. Most importantly, the movement-related changes could be mimicked by heating the animals and reversed by cooling them.

These authors subsequently showed that after compensating for temperature changes by means of passive warming, a short-lasting component of exploration-related potentiation remained unaccounted for (Moser et al., 1993c). The possibility therefore remains that learning-associated potentiation can be observed using field potential recording. However, an important lesson from the temperature studies is that learning involves many other factors than simply memory storage: in this case, physical exertion and its concomitant temperature rise. It follows that other previously reported learning-associated changes in evoked field potentials (e.g., Rüthrich et al., 1982; Skelton et al., 1987) may also be confounded by behavioral effects. In support of this, a study in which behavior was equalised between learning and non-learning groups during physiological testing (by measuring evoked responses in a different environmental condition from, and 24 h after, spatial training) failed to demonstrate a change in evoked response size (Cain et al., 1993). In a study reported in greater detail in the next section, we also have failed to find changes in perforant path evoked response size 24 h after watermaze training (Fig. 3: squares). Dissociating the possibly subtle changes in plasticity related evoked field potential size from the large non-specific changes produced by associated behaviors and affective states presents a formidable task, at least in the domain of field potential recording.

In vitro techniques may circumvent some behavioral confounding problems. Green and Greenough (1986) housed rats in a complex environment and subsequently measured evoked responses in the perforant path/dentate gyrus synapse in hippocampal slices taken from these animals. When the slices were investigated immediately after complex housing an increase was found in both the EPSP and population spike, although unlike LTP there was no change in the relationship between them (i.e., no E-S potentiation). This increase appeared to be independent of changes in general cell or afferent fibre excitability. When the rats were rehoused in impoverished conditions (standard laboratory cages) for the 3 weeks prior to sacrifice the responses did not differ from those of rats that had always been housed in this manner. This type of experiment confirms that the change underlying the

evoked potential increase is localised to the hippocampus. Whether or not it is related to synaptic plasticity per se remains to be determined.

Effect of learning experience on LTP

If the synaptic plasticity/learning/LTP hypothesis is correct then modulation of synaptic *plasticity* (as distinguished from strength) might produce an association between a prior learning experience and the subsequent induction of LTP (perhaps via an affect on NMDA receptor numbers or second messenger systems), independent of effects on the baseline evoked potentials themselves. Relatively few studies have looked at the effects of learning on subsequent LTP induction. Bergis et al. (1990) measured dentate evoked potentials 2 days after aversive training (a tone-footshock association) and then induced LTP, and found a considerable enhancement of LTP magnitude in the conditioned compared with the pseudoconditioned animals (who received unpredictable footshocks). These results were hypothesised to be due to an increase in synaptic plasticity caused by training (possibly by effects on the NMDA receptor), resulting in enhanced LTP.

An alternative explanation is suggested by the recent findings of several experiments in which animals were subjected to uncontrollable stress prior to LTP measurement. Foy et al. (1987) found that if rats were kept in restraining tubes for the 30 min prior to sacrifice, their hippocampal slices subsequently showed considerably less LTP than those from unrestrained controls, suggesting that stress may affect synaptic plasticity. Shors et al. (1989) found that application of electrical footshock in a shuttlebox does not impair LTP if animals are able to escape the shock at will, but profoundly impairs it in yoked controls that are subjected to the same shocks over which they have no control. This effect appears to be mediated by adrenal medullary hormones, possibly opioids (Shors et al., 1990). The similarity between the above Bergis et al. study and the latter is obvious: pseudoconditioned animals in that experiment were being subjected to an apparently random series of footshocks whereas the conditioned animals, although being unable to control the shocks, were at least being given warning prior to their administration. Thus, difference in LTP levels between pseudoconditioned and conditioned animals may instead be explained by a stress-related LTP impairment in the former, resulting from the unpredictability of the electric shocks.

We tried to circumvent this problem by inducing LTP 24 h after watermaze training (which is considered to be only mildly aversive). Eight rats were implanted with stimulating electrodes in the perforant path and recording electrodes in the dentate gyrus, bilaterally. The rats were assigned randomly to either a group receiving watermaze training followed by LTP (WM-LTP) or LTP followed by watermaze training (LTP-WM). On the day before the first baseline electrophysiology session, rats from the WM-LTP group were given six non-spatial pretraining trials in the watermaze while those from the LTP-WM group remained in their home cages. Baseline recording began the next day and was continued for 5 days. The following day the WM-LTP group underwent spatial training in the watermaze (eight trials, 2 h inter-trial interval) while the LTP-WM rats stayed in their home cages except for six pretraining trials. The next day all eight rats began an 8-day course of tetanic stimulation (50 trains daily), after which the LTP-WM rats were trained in the watermaze. Thus all rats had received the same amount of tetanization but half were trained before and half after the LTP induction phase. The results are shown in Figure 3. First, as mentioned in the previous section, there was no effect of watermaze training on the baseline evoked potentials measured 24 h later. This implies that if synaptic changes had taken place following learning, they were either too small to observe or else they averaged zero (that is, some increased and some decreased in strength). Second, although there was a very mild reduction in LTP in the WM-LTP group, this was not significant. These data indicate that watermaze training affected neither synaptic strength measured 24 h later not subsequent "LTP-ability" in the dentate gyrus. These results do not disprove the plasticity learning hypothesis, however. Perhaps the spatial memories following watermaze training were stored in some other synapses, or the changes were completed or not yet begun by the time the measurements were made. Negative results from this type of paradigm are somewhat difficult to interpret.

It is clear that investigation of the effects of prior learning on LTP induction is subject to similar pitfalls to the field potential experiments in the preceding section: that is, it is very difficult to dissociate the effects on LTP of the laying down of the memory trace, wherever that may occur, from the concomitant changes in the behavioral and affective state of the animals.

Effect of tetanization on learning

The symmetry of the postulated synaptic-plasticity/learning/LTP relationship suggests the reverse type of experiment to those described above: namely, investigation of the effects of tetanization on learning and memory. Both LTP and learning are assumed to take place on the same set of synapses. Tetanization might therefore interact with memory formation by affecting the subsequent occurrence of natural plasticity on the involved synapses.

If tetanization affects the occurrence of naturally occurring plasticity it could be either by facilitating or by occluding it. Facilitation might come about if the important factor was total synaptic strength but not the details of its distribution across the synaptic population. For example, if a pathway were simply relaying information from one brain structure to the next without synaptically processing it, then a generalised increase in the strength of its synapses might improve the performance of functions that normally use that pathway. A tetanization-induced improvement in performance was found by Berger (1984) in a non-spatial task, the conditioned eyeblink response, in rabbits. Unilateral perforant path tetanization was found to accelerate acquisition of the eyeblink response to a tone signalling an airpuff. Because lesions to the hippocampus do not impair performance on this task (Solomon and Moore, 1975), Berger suggested that the role of the hippocampus is to act as a general modulatory agent, and potentiating the synapses turns up the gain of the signal.

Most current computational models, however, assume that information is stored not in the absolute strengths of the synaptic connections, but rather in the *pattern* of these strengths as they are distributed across the population as a whole. According to these models, uniform strengthening of synapses (such as occurs after tetanization) should therefore not enhance learning and might even occlude it, especially if the synapses were driven to their maximum strengths ("saturated"). Occlusion can occur when two phenomena share a common mechanism so that the occurrence of one interferes with the simultaneous or subsequent occurrence of the second. Occlusion of learning and memory formation by LTP induction would constitute strong (though by no means conclusive) evidence that the two phenomena involved both the same set of synapses and the same plasticity mechanisms.

Occlusion of spatial learning by LTP induction in the dentate gyrus was reported in two prominent studies. The first study tested spatial learning of rats on a circular platform task and an eight-arm radial maze (McNaughton et al., 1986). First, rats were trained to learn the location of an escape hole on the circular maze. In 12 animals LTP was then induced bilaterally in the perforant path/dentate gyrus synapses while in the remaining 12 only low frequency pulses were applied. The following day the goal was shifted by 135°. On the first trial the rats navigated towards the previous goal location, suggesting that their spatial localisation abilities were intact and that they remembered where the goal had been. However, in subsequent trials the animals that had received bilateral perforant path tetanization made significantly more errors than the low-frequency controls in learning the new goal location, suggesting a long-lasting disruption of spatial learning following tetanization. A second experiment showed that LTP induction produced an anterograde amnesia lasting several days and a retrograde amnesia lasting at least 5 min. Further analysis suggested that the tetanized animals were persisting in approaching the previous goal location, suggesting as before that pre-tetanization memory and spatial localisation ability were unimpaired. In two more experiments it was shown that in addition to reversal learning, new learning was impaired (though less severely). However, performance appeared normal on the radial arm maze, a task known to require an intact hippocampus (unlike the circle maze, in which this has yet to be demonstrated).

The second study was carried out in a watermaze and extended these observations (Castro et al., 1989). Rats were given bilateral tetanic perforant path stimulation daily for 14 days in order to drive synaptic strengths to their maximum. Half these rats were trained on a watermaze task and spatial learning was assessed by removing the platform on the final trial and recording the amount of time each rat spent searching the quadrant of the pool where the platform had been located. The tetanized rats showed a profound deficit in their ability to learn the platform position. Two weeks later the remaining rats were trained on the same task while the originals were trained on a reversal. Both groups performed as well as controls, implying that the deleterious effects of LTP induction had dissipated.

The "saturation results" were powerful because they appeared to show that interference with a simple mechanism (plasticity) in a small subset of pathways could profoundly interfere with learning. While a tetanization-related learning impairment does not, by itself, prove that synaptic plasticity underlies learning (tetanization might cause temporary derangement of normal synaptic transmission, rather than plasticity), it narrows the range of possible explanations down to a small, and potentially testable, subset of possibilities. Unfortunately, however, several investigators (including those who reported the original result) have since tried and failed to replicate the Castro et al. (1989) findings (Jeffery and Morris, 1993; Korol et al., 1993; McNamara et al., 1993; Sutherland et al., 1993; see Bliss and Richter-Levin, 1993 for a review).

It could be argued that the failure of "saturation" to interfere with learning justifies the conclusion that LTP must, therefore, have nothing to do with learning. This conclusion does not follow, however, because while there are a small number of spurious reasons why LTP saturation might interfere with learning (and most of these testable), there are a very large number of possible reasons why it *doesn't* block learning. These reasons have been discussed in greater detail by Bliss and Richter-Levin (1993). Perhaps LTP was not induced in enough fibres, for example. This argument is difficult to refute since we do not yet know how many functioning perforant path fibres are needed to sustain performance on the watermaze task. Or, perhaps the synapses were not potentiated to their maximum extent, or long-term depression could have taken over as the primary information storage substrate until the synapses had regained their LTP-ability, or the wrong pathway in the hippocampal network was tetanized, and so on. Efforts are being made to address some of these possibilities—for example, Barnes et al. (1994) have replicated the finding of impaired circle-maze performance following LTP induction, although again, they failed to find an impairment of watermaze learning. They have also determined, using multiple electrodes, that tetanization at a single stimulation site indeed fails to saturate the entire perforant path, a finding that is confirmed by comparison of LTP-induced immediate-early gene activation with that triggered by electroconvulsive shock (ECS), which activates the entire hippocampus. More interestingly, administration of ECS produced both an enhancement of the evoked response (resembling LTP; see also Stewart et al., 1994) and a parallel impairment of watermaze learning, suggesting that ECS saturated LTP in a graded manner that might account for the animals' (also graded) failure to learn. However, ECS produces very widespread brain changes, and it might be that one of these changes both induced LTP *and* impaired learning, without the one necessarily depending on the other. For example, both might be similarly affected by the intensity of the associated seizure. Nevertheless, this finding does provide limited support for the saturation hypothesis. Furthermore, Moser et al. (1993a) have shown that spatial learning can be supported by just a small fraction of hippocampal tissue, suggesting that saturation would theoretically need to be very nearly complete throughout the whole structure, to produce any effect at all. This possibly accounts for the failure of the tetanically induced saturation to produce the same effects as ECS.

It appears that a negative saturation result tells us little about the mechanisms of learning because there are too many reasons why attempted saturation might not work (even if LTP *is* linked to

learning). On the other hand, while a positive saturation result provides some support for the LTP/learning hypothesis, a great deal of work would be needed to rule out non-specific confounding factors that accompanied both LTP induction and impaired learning. Until a way is found of circumventing the problems described above, the saturation approach must be treated cautiously.

Effect of manipulating synaptic plasticity on learning

Manipulations of synaptic plasticity alter the capacity of synapses to change without necessarily causing any such changes to occur. Synaptic plasticity may be directly affected using pharmacological or genetic manipulations that modulate the sequence of events responsible for the induction of plastic changes like LTP. The effect on learning of such manipulations is the source of a great deal of study at present, since the finding of predicted learning changes would support the synaptic plasticity/learning hypothesis, while the absence of such changes in the face of known blockade of plasticity would greatly weaken it. In order to target synaptic plasticity without affecting normal synaptic function (such as transmission, transmitter re-uptake, postsynaptic membrane potential and so on) it is necessary to isolate those factors that are specific to plasticity and not shared by other mechanisms. Nearly every link in the chain between pre/postsynaptic conjunctive activity and LTP expression has been investigated to assess its effects on learning. Principal among these are the NMDA receptor, the second messenger systems and RNA and protein synthesis.

Because the NMDA receptor is critically involved in the induction of one form of LTP, and does not appear to play a large part in normal synaptic transmission (Coan and Collingridge, 1985), it is an ideal candidate for a plasticity blocker with which to test the plasticity/learning hypothesis. Only studies investigating spatial learning will be considered here. The first and most prominent of these were conducted by Morris and colleagues in the watermaze (Morris et al., 1986, 1989; Morris, 1989; Davis et al., 1992) using rats in which the NMDA receptor blocker amino-5-phosphonopentanoate (AP5) was infused into either the cerebral ventricles or the hippocampus itself. In various experiments these investigators showed that rats receiving NMDA receptor antagonists under a variety of protocols could not learn either the task itself or a reversal, showing longer latencies to find the platform during training and little specificity of search on the absent-platform test. Studies using the non-competitive NMDA antagonist MK-801 have found a similar effect on watermaze performance in rats (Robinson et al., 1989) and gerbils (Mondadori et al., 1989). Using this drug, Shapiro and Caramanos (1990) have also found a deficit on reference but not working memory on a radial arm maze task. An interpretation of these experiments is therefore that NMDA receptors are being used in spatial learning (possibly formation of a spatial map).

The finding that NMDA blockade seriously impairs spatial learning has been, to date, one of the strongest lines of evidence supporting the LTP/learning hypothesis. Admittedly, this result is less precise than the saturation finding because there are more alternative explanations available (e.g., see Keith and Rudy, 1990). For example, although NMDA receptors are found most abundantly in the hippocampus, they are also found elsewhere in the brain (Monaghan and Cotman, 1985) and injection of the drugs into the peritoneum or infusion into the cerebral ventricles would allow them to exert their effects on other brain structures. Furthermore, NMDA receptors are involved in other synaptic functions than just plasticity. Such functions within the hippocampus itself include modulation of complex spiking of pyramidal cells (Peet et al., 1987; Abraham and Kairiss, 1988) and theta rhythm (Leung and Desborough, 1988). The NMDA receptor also plays an important role in many extra-hippocampal processes including modulation of sensory input (Salt, 1986), anxiolysis (Clineschmidt et al., 1982) and neural development (Kleinschmidt et al., 1987) and many others (for review, see Daw et al., 1993). Administration of NMDA antagonists produces profound sensorimotor disturbances (Tricklebank et al., 1989), an important consideration when a task with complex sensory and motor components (such as the watermaze) is being used to assess learning ability.

Impairment of performance on a behavioral task following administration of an NMDA receptor antagonist may therefore have many causes. Nevertheless, several of these alternative explanations for the AP5-associated spatial learning impairment had been isolated and at least partially excluded by means of a variety of control tasks (Morris et al., 1986; Morris, 1989) and methods of drug administration (Morris et al., 1989), and the core finding appeared, until very recently, quite robust. However, the picture has since been complicated by the finding of Morris and his colleagues that rats that had learned a spatial task in an undrugged state and in a different environment prior to watermaze training with AP5 showed no spatial deficit (Bannerman et al., 1995). In a further experiment, Bannerman et al. found that when rats were pretrained with a *non*-spatial task, their subsequent spatial learning again became NMDA-receptor dependent, suggesting that the watermaze task is composed of dissociable components, some of which are affected by AP5 administration and some of which are resistant to it. However, Saucier and Cain failed to find such a learning impairment following NMDA receptor blockade, even with non-spatially pretrained animals (Saucier and Cain, 1995). To date, then, drug-induced interference with LTP has produced mixed results, neither proving nor disproving the LTP-learning hypothesis.

Pharmacological blockade of plasticity is complicated because of the difficulty of ensuring that drugs reach only their target locations. This difficulty has been one of the driving forces behind the development of transgenic technology, which aims to sabotage plastic processes at a genetic level. Various transgenic mouse strains have been developed that lack one or more critical links in the chain involved in LTP induction, with the expectation that these animals would also be deficient in learning. Several experiments have produced promising results; for example, mice unable to express a subunit of calcium-calmodulin-dependent protein kinase II (CaMK II) are impaired on a watermaze task (Silva et al., 1992a), and slices made from their hippocampi do not express

LTP (or at least do so only erratically, Silva et al., 1992b). Mutant mice unable to express one of the genes (*fyn*) coding for tyrosine kinase show a parallel impairment of both LTP and performance on a watermaze task (Grant et al., 1992). However, it should be borne in mind that these transgenic animals were born with their defective genes, and some show developmental changes in hippocampal structure, suggesting that parallel changes in both LTP and learning may have been produced by some other derangement of function (perhaps not always visible).

Furthermore, there does not appear to be a simple relationship between expression of LTP and ability at spatial learning in mutant animals. Bach et al. (1995) found an impairment of learning in a spatial task (the Barnes circular maze) in CaMK II mutant mice. These animals were unimpaired in LTP when this was induced using standard laboratory parameters (100 Hz; Mayford et al., 1995). However, when they were tetanized at lower frequencies, closer to the theta range, they began to express depression rather than potentiation. This finding suggests that ordinary tetanic LTP might differ in important ways from the plasticity mechanisms that operate during learning, and that plasticity evoked with lower frequencies of stimulation might be a more appropriate way of testing the plasticity learning hypothesis. The question then arises: how many different stimulation paradigms must be tested before it can be concluded that a given mutant will never express LTP?

Mutant mice deficient in the γ isoform of protein kinase C show profoundly impaired LTP in CA1, and yet are only mildly impaired on spatial tasks and contextual fear conditioning (Abeliovich et al., 1993a, b), both of which are hippocampally dependent. Similarly, Nosten-Bertrand et al. (1996) have found normal watermaze learning in Thy-1 deficient mutant mice, which show impaired dentate LTP. These results at first glance look damaging for the LTP learning hypothesis, and indeed, Nosten-Bertrand et al. concluded that "LTP in the entorhinal projection to the dentate gyrus may not be necessary for this form of spatial learning." However, it appears that under some circumstances, LTP in mutant mice can be "rescued." Abeliovich et al. found that LTP returned when a priming pulse was applied prior to tetanization. Arguably, naturally occurring neural activity more closely resembles primed tetanization than standard tetanization. Similarly, Nosten-Bertrand et al. found that disinhibition of the dentate gyrus restored its potentiability in mutant mice, suggesting that their abnormality was one of local network inhibition rather than plasticity per se. This is important because levels of inhibition are greatly different in freely moving animals (due to movement-correlated theta modulation via the medial septum). Perhaps Thy-1 mutant mice exhibit normal LTP when awake, possibly explaining why they learn normally. No transgenic studies have been conducted to date in awake animals, and it may be that when this is done, some of the apparent discrepancies in the literature will begin to resolve themselves.

These findings nevertheless raise a serious question about the interpretation of negative results in the transgenic studies: namely, if LTP is impaired under some conditions but not others, how can we ever know that there is not some hypothetical condition (such as might occur, for example, during learning) under which LTP could be expressed normally by a mutant animal whose tetanic LTP is impaired and whose spatial learning is intact? In other words, how could a transgenic study ever falsify the LTP/learning hypothesis? As with the saturation and drug studies, it appears that at present, both positive and negative transgenic results can be accommodated within either the LTP = learning or the LTP ≠ learning frameworks.

Correlation between evoked potential change and learning

If both learning and the change in size of the evoked potential depend on underlying synaptic plasticity then correlations would be predicted to occur between them. The first such correlation was observed by the authors of the original LTP studies, who noted that the long time course of LTP persistence was considerably closer to that required for a memory mechanism than other neurophysiological plastic changes such as post-tetanic potentiation (Bliss and Gardner-Medwin, 1973). An extension of this correlation to variation in learning ability was made by Barnes (1979) in a comparison of LTP and spatial learning in young and old rats. Young rats learned the circular platform task faster and with fewer mistakes than the old rats. A single subsequent tetanization session produced the same amount of LTP in both young and old rats but when the tetanization was repeated daily the old rats showed a slower accumulation, and by the third consecutive tetanization day had gained significantly less LTP, apparently because overnight LTP decay became markedly slower in the young rats but remained fast in the old rats. On the basis of these findings Barnes suggested that repetition of the stimulation that evoked plastic changes in the synapses somehow prolonged the time course of those changes, producing an accumulation of EPSP LTP that reflected the amount by which the durability of the plastic changes was increased. The same animals that showed the greatest accumulation of LTP also showed the greatest retention of the spatial task after repeated training trials. She postulated therefore that the durability of hippocampal synaptic plasticity may underlie retention of the spatial task. In a subsequent study, Barnes and McNaughton (1985) further showed that in young and old rats, the ratio of LTP decay between the two groups matched the ratio of memory retention.

Several other correlations have been found between LTP induction and learning. For example, both LTP and conditioning are facilitated by post-trial stimulation of the reticular formation (Laroche and Bloch, 1982). Deupree et al. (1991) found a strong within-animal correlation between the magnitude of LTP induction and spatial learning ability in young and old rats. Standard stimulation parameters (50 pulses at 100 Hz) were used to induce LTP in the hippocampal slices of animals whose spatial learning ability had been determined in a watermaze prior to sacrifice. They failed to find any differences between the magnitude of subsequent potentiation in young and old animals. However, when LTP was induced using weaker stimulation (four pulses) the old animals showed less potentiation at 1 min (short-term potentiation, STP). Most importantly from the point of view of the plasticity learning hypothesis, within-animal correlations of

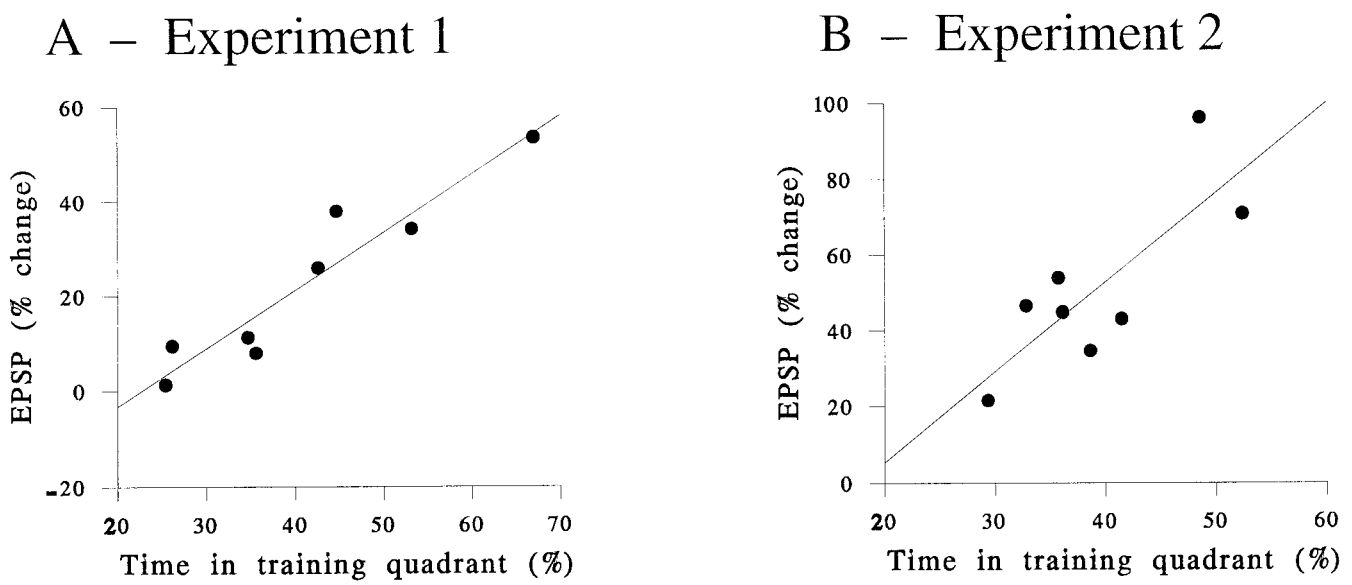

FIGURE 4. Comparison of EPSP LTP and learning for two experiments in which LTP was induced to asymptote prior to watermaze training. There was a significant correlation between LTP magnitude at asymptote, and subsequent learning ability.

prior spatial performance with both STP and LTP revealed greater enhancement in animals with better spatial learning ability, regardless of age.

We found a somewhat similar correlation between LTP and learning ability in the LTP saturation study discussed earlier (Jeffery and Morris, 1993). Although no saturation-related learning impairment was demonstrated in our experiments, rats showing superior watermaze performance showed higher levels of LTP following the saturation protocol than those that were poor learners (Fig. 4). Because the overall performance of tetanized rats did not differ significantly from controls, this finding could not represent a tetanus-induced facilitation of learning. Rather, it appears that the rats that were best able to gain LTP were also the best able to learn the watermaze task. This is a striking association and suggests that something about dentate synapses was related to both learning and LTP-ability, and suggests further that it may be their NMDA-receptor-associated plasticity. This finding therefore appears to provide strong support for the plasticity learning hypothesis.

However, a further study in which LTP was compared with prior watermaze performance (to exclude the possibility that LTP was facilitating learning) showed that this correlation only held when strong test pulses were used to evoke the responses (Jeffery, 1995). If weak pulses were used (to elicit the test responses: *not* to induce LTP) then the correlation reversed in sign: that is, poorer learners showed *better* LTP (Fig. 5).

The explanation for this somewhat puzzling finding appears to lie in the way LTP is quantified by measuring evoked responses. It was found that in this experiment, the magnitude of LTP observed by measuring the responses to test pulses before and after tetanization varied in a highly systematic manner with the strength of the test pulses. Specifically, the greater the LTP measured using strong test pulses, the smaller it was when measured with weak pulses. This result remains to be explained, but it does suggest that the measure of LTP obtained with a single test pulse located around the mid-range of the evoked response size (where they are typically measured) is a very inaccurate measure of the "real," synaptic LTP. It seems likely that the smaller the test pulses, the better the measure, with the y-intercept value giving the most accurate picture. This finding implies that using field potentials to measure synaptic events may present interpretational difficulties, and suggests that caution is needed when trying to infer a quantitative estimate of synaptic LTP from population responses.

If it is true that the y-intercept value of LTP gives the most accurate picture of synaptic potentiation, then it appears from the above results that poor learning rats show better LTP (a higher y-intercept) than good learners, the exact reverse of what was found in the previous study and the opposite result to that which would be predicted by the LTP/learning hypothesis. However, it is possible to devise plausible hypotheses to explain this apparently paradoxical set of findings. For example, perhaps LTP is coding not spatial learning per se (the learning of spatial locations with respect to cues) but rather a function such as search strategy, so that rats in which prolonged and robust LTP is easily induced are more likely to perseverate in their searching, whereas those in which LTP is hard to induce show a more flexible and dispersed search pattern. Alternatively, perhaps rats spending little time searching the training quadrant during probe trials have indeed formed an accurate spatial representation, but are reluctant to spend too much time searching for an obviously absent platform. Rather than being poor learners, as was supposed, these animals may in fact be *better* learners than rats persevering in searching the training quadrant. As long as explanations like these can be recruited to explain data that seem to contradict the LTP learning hypothesis, it is clear that not enough is known about the

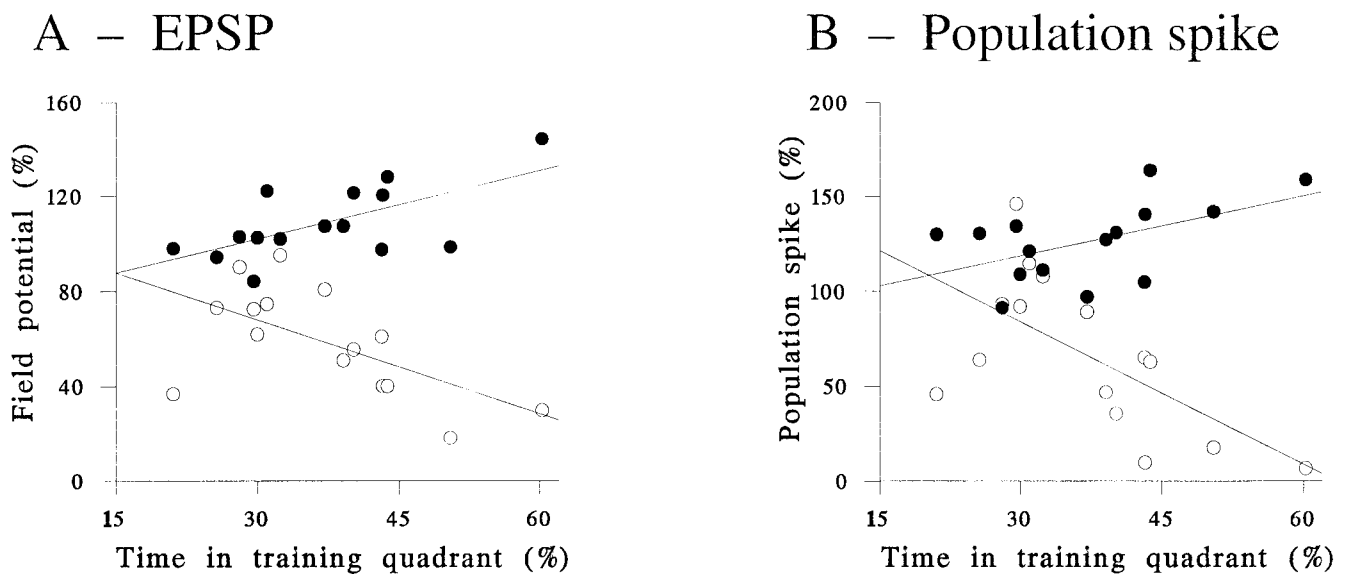

FIGURE 5. Correlation between evoked potential size and spatial learning ability when LTP is measured using weak pulses (200 μA; open circles) or strong pulses (1,000 μA; filled circles). A correlation between learning and LTP induction that was positive when strong pulses were used, reversed in sign when weak pulses were used.

subcomponents and anatomical substrates of spatial learning to sensibly constrain the interpretations of LTP findings.

Another way in which correlational studies may be useful is in comparing the biological substrates of LTP and learning. If an LTP-like mechanism underlies learning, then similar biochemical changes should follow from induction of either, and if enough similarities are found then this may constitute significant support for the LTP learning hypothesis.

One biochemical change that appears to be common to both LTP and learning involves glutamate release from presynaptic terminals in the dentate gyrus, which is increased after both LTP induction (Bliss et al., 1986) and watermaze learning (Richter-Levin et al., 1995). Glutamate release also, like LTP, correlates with spatial learning ability in individual aged rats (Zhang et al., 1991). Another important LTP-associated biochemical change involves the translocation of protein kinase C (PKC) from the cytosol to the membrane, a process that sets in motion a chain of intracellular events thought to result in the establishment of long-lasting synaptic changes (Akers et al., 1986). Bank et al. (1988) found translocation of PKC in CA1 pyramidal cells following classical conditioning in the rabbit, leading to the hypothesis that PKC changes might also be seen following spatial learning. In support of this, Wehner et al. (1990) found a striking correlation between PKC activity and watermaze ability in different strains of mice. Olds et al. (1990) found a decrease in membrane-bound PKC following watermaze training in rats, which they suggested reflected increased inactivation of PKC following translocation. However, these changes were only seen in the CA3 subfield, and also occurred following visual discrimination, which is normally a hippocampal-independent task (Morris et al., 1986). Clearly, the alterations in PKC following classical conditioning and spatial vs. non-spatial discrimination are complex, and may reflect the involvement of different isoenzymes in different tasks. Furthermore, the involvement of PKC in learning-associated synaptic strength change remains to be established. Nevertheless, the findings of parallels between biochemical changes following learning and those following LTP provide some support to the LTP learning hypothesis, even though they cannot prove it.

Conflation of learning experience with tetanization

Finally, it is worth discussing some unusual experiments in which the two halves of the synaptic plasticity/LTP/learning scheme have been amalgamated, by making the tetanization process itself the conditioned stimulus (CS) in an associative learning paradigm.

Laroche et al. (1989) used a perforant path tetanus as the CS to signal footshock in a conditioned suppression task. They found that rats in which robust LTP developed learned the task whereas those in which LTP development was blocked, either by subthreshold tetanization, infusion of an NMDA antagonist or simultaneous tetanization of convergent inhibitory inputs, failed to do so. In a further experiment Doyère and Laroche (1992) showed that retention of the task correlated inversely with the decay rate of LTP, so that rats in which LTP returned rapidly to baseline performed poorly when retested on the task some time later whereas those in which potentiation persisted retained the task well. This parallel behavior of LTP and memory is very striking, and could provide support for the plasticity learning hypothesis, except for the following problem: because the CS produced LTP in the pathway being tested, it may, in effect, have strengthened itself—that is, it may have increased its own salience. Any changes in learning that took place following changes in the stimulus

properties cannot therefore be dissociated from plasticity-related changes. It is as if a very faint tone in a tone-footshock task had been made louder for some animals, who naturally would then find it easier to learn about it. Since the result can be explained either with or without invoking the presence of naturally occurring perforant path plasticity, it could be argued that no firm conclusions can be drawn about *normal* learning from the finding of improved learning in animals gaining LTP in this task.

This problem can be expressed more fully as follows: if learning *does* involve an increase in the "transmissibility" of a stimulus as it progresses through the nervous system, then the end result is the same from inducing LTP in a pathway as from an external increase in salience such as turning up the loudness of a sound or the brightness of a light (that is, an increase in responding). However, in the first case the increase in transmission takes place at a specific point along the pathway of the processed stimulus, and this specific point is the place at which the memory could be said to be being stored (according to Hebb's hypothesis). Changes in transmissibility at this point (for example, by LTP) could therefore be said to be true changes in memory. In the second case, the increase takes place outside the nervous system and does not constitute memory. The problem with the tetanization-as-CS studies discussed above is that while they introduce an artificial increase in transmissibility, it is not clear whether this comprises the first kind of change or the second. If it is the first: that is, if memory really *is* stored by the same perforant path-dentate synapses that are being tetanized, then these experiments are truly tampering with memory at a synaptic level. However, if they belong to the second class, an increase in the gain of the signal *before* it reaches the place where it is to be stored, then these experiments are logically equivalent to turning up the lights. The difficulty is that we cannot know how to interpret them until we know the very thing that they were designed to find out—where and how the memory trace is being laid down!

This interpretation could be refuted if it could be shown that the CSs (that is, the tetani) evoked equal responses in both potentiated and unpotentiated animals. Some support for this defence can be found in the fact that following application of tetani to the perforant path, there is a short-lasting pre-synaptic potentiation of *all* responses, regardless of whether LTP had been induced and whether AP5 is present. This post-tetanic potentiation (PTP) may be the neural counterpart of stimulus strength. Since PTP would have occurred in response to the CS in both learners and non-learners in the Laroche et al. (1989) study, this may argue against the stimulus-salience hypothesis presented above. However, if there is a postsynaptic component to LTP expression (a question that has yet to be resolved) then potentiated animals will always show a larger response than unpotentiated animals to perforant path stimulation, even if the presynaptic component of the response was equal. In this case, it would be necessary to equalize the size of the post-synaptic responses by reducing the stimulus strengths in the potentiated animals: a risky enterprise when salience is such a crucial variable. In addition, while it may be possible to produce a quantitative equivalence of stimuli in the different groups of animals, it may be the qualities of the stimulus that are important for salience (for example, how much of an NMDA component is present).

Another argument against the salience hypothesis is that in the retention experiment of Doyère and Laroche (1992) discussed above, the first CS after the decay/forgetting interval reintroduced LTP equally in both fast-decay and slow-decay rats: that is, the fast-decay rats gained more "catchup" LTP. Thus, it could be argued that the salience of all of the subsequent CSs should be equal in the two groups, and therefore the poor performance of the "forgetting" (fast-decay) rats requires some other explanation. There are two objections to this argument, depending on whether the relevant salience is considered to be that of the very first CS of the first retraining trial, or the remaining CSs of the first (and subsequent) trials.

The first retraining CS would arrive at the dentate gyrus through an unpotentiated perforant path in the fast-decay rats, and through a still-potentiated path in the slow-decay rats. It could, therefore, arguably differ in its salience, and be better learned about by the more potentiated rats. However, if the stimuli that are relearned by the rats are primarily the remaining CSs of the first and subsequent retraining trials, then because these arrive after LTP has been reintroduced in both groups, the salience argument no longer applies. Because both the fast- and slow-decay groups reattained the same levels of LTP, the CS saliences should now be the same in the two groups. However, now the LTP = memory hypothesis cannot be supported because LTP is the *same* in both remembering and forgetting animals! The claim that the representation of the learned CS is stored as LTP of these synapses is not consistent with the differential learning of the two groups because they have been matched in their LTP levels.

It appears that any physiological change following tetanization that might be interpreted as learning might *also* be interpreted as a stimulus salience change. It is not possible to dissociate these two alternatives logically, using this type of paradigm, until we have determined the physiological counterpart of salience. Clearly, the interesting correlations produced by these experiments are complicated to interpret.

A more clear-cut case would be made if the CS consisted of low frequency rather than high frequency pulses. The finding of LTP developing when these pulses were paired with a US would be very interesting because LTP would not normally be expected to develop as a result of low frequency pulses alone. Matthies and colleagues used a lower frequency of perforant path stimulation (15 Hz) as the CS in a shuttlebox avoidance task on rats, and found an increase in the size of the EPSP in good as compared with poor learners with an associated right-shift of the EPSP-population spike relationship (Ott et al., 1982; Matthies et al., 1986). The design of this experiment circumvents some of the difficulties discussed above. Unfortunately, because the poor learners were receiving more shocks, they were therefore possibly more stressed than, or behaved differently from the good learners, suggesting that their reduction in LTP might be stress-related. This type of confounding of behavioral state or change in stimulus salience is extremely difficult to avoid in these types of experiment. A possible approach would be to demonstrate the same result using either an appetitive or an aversive task. The finding of the

same result when opposite reinforcers were used would rule out many of the non-specific behavioral and affective confounding factors in these experiments (though not all of them). To date this does not appear to have been attempted.

FUTURE DIRECTIONS

It appears that while many provocative correspondences have been found between the properties of LTP and the properties of learning, none of the evidence is sufficiently strong to justify the conclusion that they share a common underlying mechanism. For every line of supporting evidence that has been presented, a serious counterargument has been proposed, and for every counterargument there seems to be a possible rebuttal. The question therefore arises: what type of evidence would be required to settle the matter once and for all? Such a settling is important, if LTP is to be of continued use as a model of cellular memory processes.

At the heart of the LTP-learning debate lies Hebb's postulate that a synapse should increase in strength if the pre- and postsynaptic components are simultaneously active. While the Hebbian basis of LTP induction is now well understood, there exists, at present, no Hebbian experimental model of spatial learning. Given that spatial learning is clearly too complex a phenomenon to constrain the interpretation of LTP experiments, the logical next step would appear to be to look more closely at the cellular correlates of spatial learning, to see a) if they obey Hebbian rules and b) if they share properties, such as NMDA dependence, that might be expected of an LTP-like process. If such changes were observed, and furthermore shown to correspond to changes in behavior, then this would constitute significant support for the LTP-learning hypothesis.

Such an approach has already had notable success in a different but related paradigm, the phenomenon of experience-dependent plasticity of the developing visual cortex. At the time that LTP was discovered, the physiological underpinnings of visual cortical plasticity had already been extensively elucidated and found, independently, to be Hebbian in nature. It is worth describing the paradigm in some detail, as it provides a useful pointer to how a similar model might be developed in the hippocampus.

Inputs to layer III pyramidal cells of the visual cortex fall naturally into two groups, one from each eye. Most cells receive inputs from both eyes, but if the cells are deprived of active inputs from one eye by occluding the eye during a critical period of development, then they will come to receive almost all of their inputs from the non-occluded eye (Wiesel and Hubel, 1965). The preservation of inputs from the non-occluded eye obeys a Hebbian principle: those inputs that survive are those that were active at the same time as the post-synaptic pyramidal cells, and the inputs that are lost are those that were silent (from the occluded eye). With the elucidation of the properties of LTP, it has been possible to show further that this process is NMDA dependent (Bear et al., 1990), that the same cells on which these synapses are being formed can support tetanically induced LTP (Kirkwood and Bear, 1994) and that this LTP is most easily induced during the critical period for development (Kirkwood et al., 1995). Together, these findings provide strong evidence that an LTP-like process mediates the stabilization of visual cortical synapses during development. It also appears that an inverse Hebb rule, that inactive inputs should be weakened, operates to disconnect the pyramidal cells from the inputs arriving from the occluded eye.

The finding that Hebbian synaptic rules govern synapse stabilization was perhaps the most important demonstration of a link between LTP and visual cortical development. Can a similar link be drawn between LTP and spatial learning? The hippocampus is a much less well-understood structure than the visual cortex, at present, but nevertheless it is possible to see how an analogous paradigm might be constructed to determine whether hippocampal cells use a Hebbian rule to choose their inputs.

Input Dissociation: A Hebbian Paradigm for Learning by Hippocampal Cells

To test Hebb's hypothesis at the cellular level, it is necessary to be able to segregate a cell's inputs into at least two groups, so that one may be manipulated independently of the other(s) in a manner analogous to optic occlusion. The hippocampal cells whose behavioral correlates are best understood are the pyramidal complex-spiking cells of CA3 and CA1, the place cells, whose activity is highly correlated with the location of an animal in its environment. These regions of the hippocampus receive two anatomically separate inputs, one of subcortical origin (arriving via the medial septum) and one of neocortical origin. It further appears (see below) that the neocortical inputs, which presumably carry sensory information about the animal's environment, can be functionally divided into more than one group by manipulating environmental features. Thus, the minimum conditions for establishing an experimental Hebbian learning paradigm are able to be met in this structure.

Each place cell fires maximally when the animal is in a restricted portion of the environment (the cell's *place field*). The principal determinants of place cell firing are a combination of cues in the animal's environment (O'Keefe and Nadel, 1978) and movement information which tells the animal how far and in what direction it has moved recently (*dead reckoning;* see Knierim et al., 1995). Information about the cues arrives at the hippocampus from the neocortex via the entorhinal cortex, while movement information is probably largely carried by the subcortical inputs (O'Keefe and Nadel, 1978).

Recent work shows that of the range of available cues, each cell responds to only a small subset, and only when these are located at a given distance from the animal (O'Keefe and Burgess, 1996). This has led to the remarkable finding that if some of the cues are moved within the animal's environment, some cells will alter their firing accordingly (those whose determinant cues were moved) while others will respond in the original location (those whose determinants remained fixed; see also Gothard et al., 1996). In some cases, after movement of the cues a cell will actually develop *two* fields, one that stays in the original location and one that adopts a new position.

Figure 6 shows an example of the development of a double place field following dissociation of its environmental determi-

nants. A rat was foraging for food in a small box of dimensions 40 cm × 60 cm with walls 22 cm high. Figure 6A shows the location of the place field in the baseline condition, in the southwest (SW) corner of the box. When the distal room cues were masked, by switching off the room lights and drawing curtains around the box, slow rotation of the box resulted in an accompanying rotation of the place field, so that it maintained the same relative location with respect to the box (Fig. 6B). The cell was therefore either responding to the local cues in the box (such as its visual appearance, geometry and odours) or to a continuously updated record of the animal's movements since the distal cues were masked (dead reckoning), or both. However, when the same manipulation was performed with the distal cues visible, the field adopted a new position with respect to the box. This shows that local cues and/or dead reckoning were not enough to support the place field when the distal cues were present, suggesting that this cell was receiving an input from the distal cues, and furthermore, that this input was able to override the proximal cues when it was placed in conflict with them.

That inputs to place cells can be dissociated this way, and found to differ in the strength with which they drive the cell, opens up the possibility of deriving a paradigm for the experimental induction of plastic changes in place fields. Hebb's hypothesis predicts that if a cell receives both a weak and a strong input, then coactivation of the weak input with activity of the cell (driven by the strong input) should produce an increase in the strength of the weak input. In this light it is interesting to note that for the cell described above, the new field driven by the distal cues retained its new relationship to the proximal cues, even when the original position of the box was restored (Fig. 6E). While it is premature to conclude that this represents an example of Hebbian modification, nevertheless the observation of plasticity of place fields in situations where their inputs are being functionally dissociated is intriguing.

Although the paradigm described above relied on indirect manipulation of large numbers of inputs by changing the environment, a similar principle could be used to investigate synaptic changes at a cellular level. To examine the connections between single cells in a behaving animal, it is necessary to record simultaneously from two synaptically coupled cells, something that can only be achieved in practice while recording from large numbers of differentiable cells. The strength of a cell-to-cell connection can be measured indirectly by cross-correlating the activity of one cell with the activity of the second. If the cross-correlation peak is tall and of relatively short latency, this suggests that activity in the first cell is helping to drive activity in the second, the height of the peak reflecting the strength of the connection. If Hebbian principles govern the establishment of these connections, then inducing the two cells to fire simultaneously (or nearly so) should result in an increase in the strength of the connection and hence the height of the cross-correlation peak. A similar method has been used to suggest that cells that were simultaneously active during wakefulness (because they had overlapping place fields) are more highly cross-correlated during subsequent sleep periods (Wilson and McNaughton, 1994; Skaggs and McNaughton, 1996). However, these cells were not synaptically coupled, and the determination of true Hebbian synaptic learning would require that a similar observation be made between cells that are shown to be connected, perhaps via antidromic stimulation. Nevertheless, these types of single unit recording methods may in future be of great use in examining the

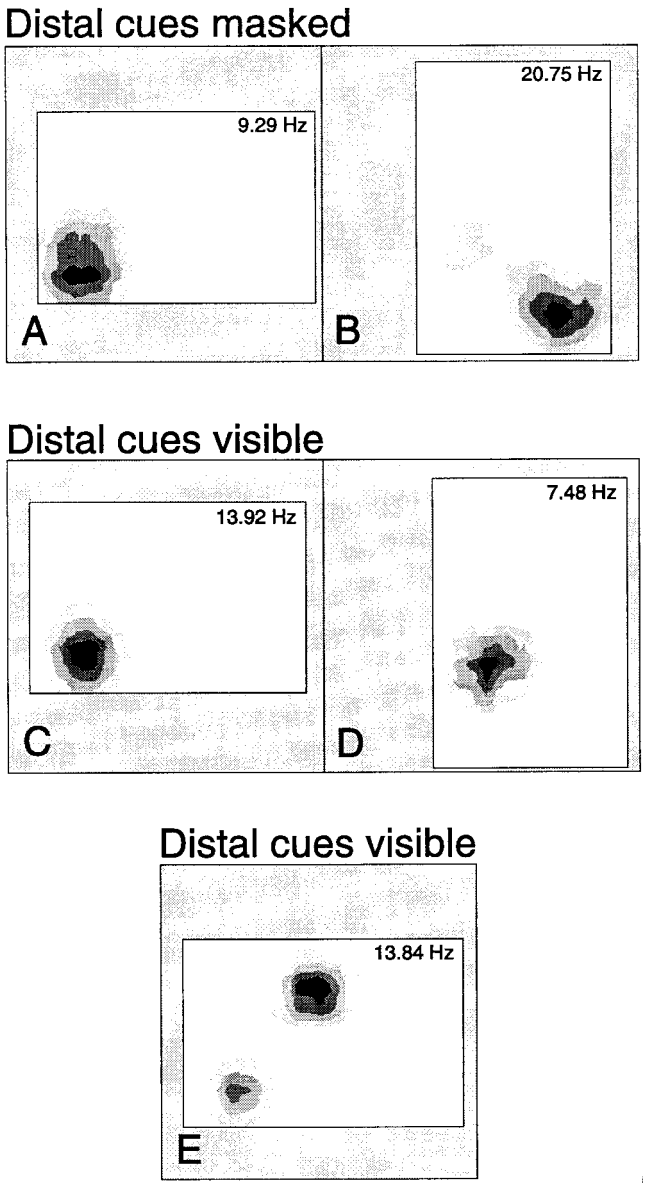

FIGURE 6. Dissociation of environmental influences on hippocampal place fields. A: Initial position of the place field of a single hippocampal complex spiking cell. The rectangle indicates the outlines of a box 60 cm × 40 cm × 22 cm high, in which a rat foraged for 2 min. Each instance of the cell's firing was recorded and superimposed on the position of the rat at the time, yielding the contour plot shown by the grey scale (black = max. firing rate, shown by the number in the top right-hand corner of the rectangle). B: When the box was screened from the outside room by means of curtains, and rotated slowly 90° counterclockwise in near-darkness, the place field also rotated, maintaining a constant position relative to the box. C,D: When the sequence of moves was repeated in the light with the curtains open, the field did not rotate with the box but adopted a new position within it, suggesting that the now-visible room cues were now the dominant influence on its firing. E: When the box was restored to its original position 20 min later, both the original and the new components of the field were now present.

question of whether an LTP-like process governs synaptic modification in the hippocampus. In particular, because neuronal stimulation is natural rather than artificial, the host of problems surrounding electrical stimulation and tetanization methods (such as abnormal recruitment of local inhibition) can be avoided using this type of methodology.

CONCLUSION

The conclusion of the present article is that while the technique of LTP induction is an invaluable tool for investigating the cellular basis of synaptic plasticity, both LTP and spatial learning are too complex for direct meaningful relationships between them to be inferred, given our current level of knowledge. In other words, the LTP/learning hypothesis is too under-specified usefully to constrain interpretation of behavioral/physiological correlations and so the hypothesis is unfalsifiable. Clearly, it is necessary to find a reduced form of the hypothesis.

One possibility is to look for a Hebbian model of spatial learning at the physiological (representational) level. The pathways contributing to place-specific CA1 complex spike firing (which is tightly coupled to behavior) are relatively well-known. If a plastic process contributed to the determination of place fields then it probably took place in one of these pathways. The LTP hypothesis could then be reformulated (using the abundant physiological data on its properties as a basis), as a set of more highly specified questions: 1) Do NMDA-dependent changes in neuronal connectivity contribute to environmentally determined changes in place cell firing? and if so, 2) Do such changes obey the same rules of associativity, co-operativity and input-specificity as LTP? 3) Do these changes involve the same second messenger systems as LTP? 4) Are these changes correlated with appropriate changes in the behaviour of the animal?

Finding the answers to these questions would set us a great deal further along the road to establishing whether an LTP-like process mediates the spatial learning function of the hippocampus.

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