REVIEW

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Learning from LTP: A Comment on Recent Attempts to Identify Cellular and Molecular Mechanisms of Memory

Abstract

In recent years disappointing evidence has emerged regarding all main lines of evidence supporting connections between long-term potentiation (LTP) and memory. The history of this research, including studies focusing on synaptic alterations following learning experience, on saturation of LTP, and on pharmacological and genetic manipulations of LTP, are discussed briefly and interpreted in light of their observed and inherent limitations. Other approaches, aimed at showing a continuity of plasticity from molecular to synaptic to circuit and systems levels of analysis, are highlighted as potentially more compelling future directions for this research.

Introduction

Why all the excitement about long-term potentiation (LTP) and memory? In my view there are two major reasons LTP has received such a warm welcome from memory researchers. First, LTP has a set of characteristics like those we would want of memory (Morris et al. 1991). It is induced rapidly by as little as a single short burst of afferent activity and involves a lasting incremental synaptic response that reflects increased efficacy of transmission. And the major form of LTP studied, *N*-methyl-D-aspartate (NMDA)-dependent LTP, has the key properties outlined by Hebb (1949) for a neural memory mechanism—the conjunction of presynaptic and postsynaptic activation—that underlies “associative” learning. Second, beyond these similarities to memory, LTP provides cellular physiologists with a tractable model of memory, an experimental preparation that seems to contain the elemental processes of memory and is amenable to cellular and molecular manipulations and measurements. Brief bouts of afferent activation result in lasting potentiation—or with differently timed activations the converse, depression—in both the field excitatory postsynaptic potential (EPSP) and the population action potential, reflecting as much as a twofold alteration in efficacy of the driven pathway. Recent discoveries elucidating the physiological and molecular properties of synaptic modifications that constitute LTP have made this model almost too compelling, so attractive that it would be a shame if it turned out not to be a memory mechanism (e.g., Stevens 1996).

With these powerfully attractive features in mind, much research has gone forward to validate the LTP model of memory by determining the extent to which LTP and memory share the same cellular and molecular properties. Issues and concerns about the connection between LTP and memory have been raised previously (e.g., Hargreaves et al. 1990; Keith and Rudy 1990; Bliss and Richter-Levin 1993; Eichenbaum and Otto 1993; Diamond and Rose 1994; Andersen and Moser 1995; Andersen and Trommald 1995; Eichenbaum 1995; Cain et al. 1996). Here I will not try to provide a comprehensive critique of this body of work. Rather, I will comment briefly on the mixed history of success and limitations in

strategies taken so far, and then offer some reflections on future research directions that seem most useful from the perspective of a behavioral neuroscientist. The take-home message of this commentary is that the major approaches used to date have failed to provide compelling evidence of a connection between LTP and memory, but newer, more sophisticated approaches may yet succeed.

Common Bases of LTP and Memory?

Several relatively direct approaches have been pursued in attempting to demonstrate that LTP and memory share common physiological and molecular bases. Following this research has been like riding a roller coaster in that initial studies using each of several approaches charge beyond legitimate reservations to produce exciting positive results. But then, in each case, disappointing new data has emerged calling into question the initial findings and suggesting that the original reservations were well grounded. These efforts can be categorized into three general approaches: demonstrations of changes in synaptic physiology as a consequence of learning experience (“behavioral LTP”), attempts to prevent learning by “saturation” of hippocampal LTP, and attempts to alter learning performance by pharmacological or genetic manipulation of LTP induction.

BEHAVIORAL LTP

Do real learning experiences produce changes in synaptic physiology like those that occur with LTP? Seeking changes in synaptic physiology consequent to learning is an ambitious and optimistic approach because one might well expect the magnitude of synaptic changes observed in gross field potentials would be vanishing small—a virtual “needle in a haystack”—following any normal learning experience. In addition, most computational neuroscientists believe that learning involves changes in synaptic efficacy in both the positive and negative directions. The expected result is primarily a change in the distribution of potentiated and depressed or depotentiated synapses with potentially no overall shift in the evoked field potential profile.

Addressing the first of these concerns by using powerful and extended experience as the learning event, the initial reports showed enhancement of both excitatory synaptic potentials and population spikes after different types of learning experience. The early studies included one by Green and Greenough (1986), who examined several aspects of synaptic physiology in hippocampal slices taken from rats who had been exposed to long-term enriched environmental experience. Similar results were obtained in intact animals following extended environmental enrichment in the whole animal preparation (Sharp et al. 1985) and following different types of specific conditioning experiences (Ruthrich et al. 1982; Weisz et al. 1984; Skelton et al. 1987; see also Hargreaves et al. 1990).

Following these early studies, reports of observable changes in synaptic physiology following brief exploration of a novel environment (Sharp et al. 1989) generated considerable excitement, although even from the outset there were a number of unsettling features of these observations. It was not clear how closely related the synaptic changes were to real learning and the changes did not last very long. More concerning was that, unlike LTP, the population EPSP and spike changed in opposite directions. The EPSP was enhanced, whereas the population spike was diminished. This discrepancy was interpreted as a reflection of

widespread strengthening of synapses including mostly those on inhibitory interneurons, leading to the overall diminished population spike. Following on this favorable interpretation, a succeeding study confirmed the findings and provided some controls for possible influences of attention and behavior (Green et al. 1990). However, more recently Moser and colleagues (1993) showed conclusively that the observed EPSP and population spike changes were not attributable to learning experience, but rather to temperature variations consequent to motor activity associated with exploration. They showed that both the enhancement of the EPSP and the reduction in the population spike correlated closely with local temperature changes in the hippocampus, and both effects could be reproduced or inverted by heating or cooling the animal, respectively. In addition, the effects of brain temperature could be observed either in or out of training situations, both in the hippocampus and elsewhere in the brain. Moreover, brain cooling that resulted in a slowing of dentate field potentials did not affect spatial learning (Moser and Andersen 1994), suggesting that fluctuations in synaptic efficacy occur frequently and present a major form of “noise” that must be overcome by some sort of normalization during information processing. In a thorough study of the synaptic potentials and population spikes, Moser et al. (1994) concluded that most of the changes in both types of field potentials could be explained by variations in temperature, motor activity, and electroencephalograph (EEG) state, with a small residual that could reflect learning. Perhaps this is the needle in the haystack. However, even this small synaptic alteration persists for only ~30 min, too briefly to support consolidation periods presumed to be mediated by the hippocampus (Winocur 1990; Kim and Fanselow 1992).

SATURATION OF LTP

Another approach that generated initial excitement was the effort to block learning by saturating, that is, driving to asymptote, all of the excitatory synapses in the dentate gyrus before training. This approach also involves significant optimism to override several obvious concerns. Is it really possible to saturate all the synapses in the hippocampus, even in a single stage of the hippocampal circuit? Is information processing (as contrasted with plasticity) within the hippocampal network fully normal following the intense stimulation protocol that involves 10-fold repeated 400-Hz bombardment each day for two weeks (see McNamara et al. 1993)? In addition, would not such a powerful manipulation of synaptic weights influence memory codes currently stored in the hippocampus as well as its target structures? Early studies ignored these potential complications and indicated that saturation of the perforant path synapses resulted in severely impaired new learning and spared learning accomplished previously in the normal state (McNaughton et al. 1986). In addition, succeeding experiments showed that learning capacity returned when synaptic efficacy levels dropped back to baseline (Castro et al. 1989). However, the excitement was dashed by several investigators who found no effect of saturation across a variety of experimental protocols (Cain et al. 1993; Jeffery and Morris 1993; Korol et al. 1993; McNamara et al. 1993; Sutherland et al. 1993). Subsequent efforts showed that impairments can be observed following saturating stimulation under limited circumstances (Barnes et al. 1994), but this direction of research has not been pursued vigorously.

PHARMACOLOGICAL
BLOCKADE OF LTP

Perhaps the most compelling and straightforward data on a potential connection between the molecular basis of LTP and memory come from experiments where a drug or genetic manipulation is used to block LTP and, correspondingly, prevent learning. Here again there was the need for optimistic assumptions. It had to be assumed that the drugs were selective for plasticity and not normal information processing in the brain, and that they would knock out a critical kind of plasticity. These assumptions were accepted based on demonstration of selective effects of drugs such as AP5 (D-2-amino-5-phosphonopentanoate) that block the NMDA receptor, preventing LTP while sparing normal hippocampal synaptic transmission (e.g., Bliss and Lynch 1988). To the extent that the role of the NMDA receptor is fully selective for plasticity, one could predict these drugs could prevent new learning and still not affect nonlearning performance or retention of learning normally accomplished before drug treatment. Consistent with these predictions, some of the earliest and strongest evidence supporting a connection between LTP and memory came from demonstrations that a drug-induced blockade of NMDA receptors prevents new learning (Morris et al. 1986). More recent evidence extends this connection to other brain pathways (Kim et al. 1991) and to targeted genetic manipulations showing that blocking the cascade of molecular triggers for LTP also results in severe memory impairments (e.g., Grant et al. 1992; Silva et al. 1992a,b). Complementary reports indicated that drugs that enhance the induction of LTP also facilitate learning (e.g., Staubli et al. 1994).

However, some experiments showed that a fraction of learning survived even a total block of capacity for LTP (Staubli et al. 1989; Davis et al. 1992). Other studies showed that drugs that increase NMDA-dependent LTP can result in improvements in memory (Mondadori et al. 1989; Weiskrantz and Mondadori 1991). Moreover, two newer experiments provide converging evidence of intact hippocampal-dependent learning even when the capacity for hippocampal LTP is blocked fully (Bannerman et al. 1995; Saucier and Cain 1995). These studies showed that blocking NMDA-dependent LTP does not necessarily prevent the central component of water maze learning, that is, the encoding of a new spatial map. This demonstration was accomplished by isolating new spatial learning from the acquisition of more general task knowledge when animals were provided in advance with background swimming skills and experience in a water maze. Such "pretraining" was found to protect against the otherwise detrimental effects of an NMDA-receptor blocker on new spatial learning. By one interpretation, hippocampal NMDA receptors may be critical for learning a spatial strategy but not for encoding particular maps (Bannerman et al. 1995). Alternatively, pretraining may merely overcome the motor side-effects of NMDA-receptor blockers by providing preliminary acquisition of swimming skills (Saucier and Cain 1995).

**Why Attempts to
Connect LTP and
Memory Have So
Far Failed**

The findings from each of the above described approaches do not prove LTP and memory do not share the same bases, and these studies leave some room for continued optimism by the faithful. In the studies on changes in synaptic efficacy, the experiments that controlled for temperature and other general effects show the expected changes after extended experience (Green and Greenough 1986) and small changes of both the field EPSP and population spike in the same direction as LTP

after brief experiences (Moser et al. 1994). LTP saturation may have the expected effect in limited circumstances (Barnes et al. 1994). Even the recent studies that showed learning despite LTP blockade can be given an optimistic interpretation that hippocampal LTP is critical for learning something about space, the extent of which may depend on previous experience (Shapiro and O'Connor 1992; Bannerman et al. 1995).

Nevertheless, we cannot take the recent pattern of disappointing results lightly, and with the benefit of hindsight, we can see some reasons why they might have failed. First, there have now been demonstrated multiple forms of LTP, some of which are not dependent on the NMDA mechanism (e.g., Jaffe and Johnson 1990; Kullman et al. 1992; Castillo et al. 1994), suggesting there may be a variety of parallel mechanisms that can support increased efficacy in pathway that represents associations, and therefore parallel ways to mediate memory performance. If this is indeed the case, then, to the extent that some experimental manipulations are fully selective for only one plasticity mechanism, experiments aimed to show a critical role seem doomed to fail. For example, the CA3 mossy fiber synapse demonstrates a form of LTP that is not NMDA-dependent (e.g., Staubli 1992), and the CA3 cell population is thought by some to be the best example of an associative memory network. Drugs that selectively block NMDA-dependent LTP would not prevent information from getting into or out of the CA3 network. Therefore, it is entirely possible that changes in the CA3 network could support substantial hippocampal-dependent learning capacity, even in the absence of functional NMDA receptors in the hippocampus.

Second, it has also become clear that there are different forms of memory mediated by distinct brain circuits, and these memory systems have different associational and temporal properties (e.g., MacDonald and White 1993). Therefore, when an experiment reports that memory is or is not blocked by a manipulation of LTP, the results are meaningful only in the context of where in the brain the LTP manipulation is effective and which brain system supports that kind of memory. This consideration may go far to explain why saturation-like hippocampal stimulation (Berger 1984) and pharmacological treatments that block hippocampal LTP (Mondadori et al. 1989; Weiskrantz and Mondadori 1991) can result in the facilitation of learning mediated mainly by nonhippocampal circuits and where hippocampal representations may only interfere (McDonald and White 1995). Considerations of different forms of plasticity and multiple memory systems indicate we have to be much more sophisticated when assessing the role of LTP in memory performance.

Third, even in the majority of experiments that limit consideration to hippocampal-dependent learning and LTP in the hippocampus, there is the general difficulty in distinguishing the effects of a manipulation that results in hippocampal malfunction from one that selectively blocks hippocampal plasticity. Therefore, even in principle the blocking of hippocampal plasticity and blocking overall hippocampal function are expected to have identical selective consequences: Both are expected to interfere with long-term retention of a particular kind of memory and neither is expected to interfere with normal perception, motivation, motor performance, memory for some types of information, or short-term memory of any type. Consistent with these expectations, in nearly every experiment to date blocking hippocampal LTP results in the same pattern

of deficit and spared function as observed after explicit hippocampal damage, with the exceptions that physiological or pharmacological blockade of hippocampal LTP is temporary and may be less effective than an overt lesion. This consideration calls into question the premise that drugs or genetic manipulations that block LTP spare normal hippocampal information processing. Our acceptance of the view that NMDA-receptor blockers are selective for hippocampal plasticity relies not on any functional dissociation, but rather solely on the observation that the drugs or genetic manipulations do not affect synaptic transmission as revealed in evoked potential protocols. It is important to remember that large-scale evoked field potentials never actually occur during normal information processing. The data available at this time simply do not allow us to conclude that other more relevant patterns of hippocampal information processing (e.g., EEG, single-cell firing patterns) are fully normal under the influence of drugs such as AP5.

In sum, we are faced with two major dilemmas in current research on LTP and memory. First, approaches that view memory and LTP as two unitary phenomena that can be linked directly underestimate the complications that arise from our current understanding about multiple forms of LTP and multiple forms of memory. The capacity for memory is likely supported by a variety of cellular mechanisms spread across several parallel circuits. Knocking out one molecular mechanism or even all the functions of a particular memory system can leave intact several alternative support mechanisms. Therefore, memory may be very resourceful in finding a way to help behavior adapt despite selective knockouts of one route or means of plasticity. Studies showing the selective involvement of NMDA receptors in particular forms of memory offer support for this view (Shapiro and O'Conner 1992), even as they complicated our efforts to find the memory mechanism.

Second, to the extent that we focus on plasticity in the hippocampus, we need desperately to find a way to distinguish hippocampal information processing from hippocampal information storage. Whatever computations hippocampal circuitry performs, the results may be so intertwined with hippocampal contributions to memory storage that the two may not be distinguishable by any functional measure. Yet unless we succeed in making this distinction, there will be no compelling way to prove that a manipulation targeted at blocking LTP does not in fact result in a "sick" hippocampus. For those who seek a single, simple memory mechanism in hippocampal LTP, I fear they are almost sure eventually to join Lashley (1950), who concluded from his search for a simple and singular memory circuit that "learning is just not possible."

Future Directions for Research on LTP and Memory

I have suggested in other brief comments that the future is grim for those who seek the short cut from molecular and synaptic plasticity mechanisms straight to behavioral memory (Eichenbaum and Otto 1993; Eichenbaum 1995). Instead, the long view in which the aim is to demonstrate a continuity of phenomena holds more promise for a full understanding of the mechanisms of memory. The most compelling evidence for enhancing the connection between LTP and memory will, in my view, highlight the level of neural processing intermediary between the intracellular events and behavioral phenomena. Such evidence would focus ideally on a specific memory system shown to be both necessary to support a particular type of memory performance and sufficient for this

type of memory in the absence of normal function of other known memory systems (e.g. LeDoux 1991; MacDonald and White 1993). In addition, the evidence would focus on distinguishing between normal neural coding schemes that reflect perceptual, motor, and attentional processing before and during learning and alterations in these codings consequent to learning. Therefore, it is critical that we find ways to show real neural activity patterns that bear similarity to those effective for inducing LTP, as well as changes in neural activity associated with learning that would be predicted by alterations in synaptic weights.

Examples of this approach are already pursued, at least in preliminary ways. One strategy is to reduce the gap between the pattern of afferent stimulation that is typically used to produce LTP and normal patterns of activity in the hippocampus and elsewhere. This approach relies on recent findings about stimulation parameters for producing LTP, showing that potentiation is induced preferentially by electrical stimulation that is based on three separate but related patterns of naturally occurring cell activity. LTP in CA1 is induced preferentially by high-frequency bursts of stimulation (four pulses at 100 Hz) repeated at 5–10 Hz (Larson et al. 1986), and can be induced by a single burst if another burst (Larson and Lynch 1986) or single pulse (Rose and Dunwiddie 1986) precedes that burst by 130–200 millisecc (i.e., at latencies that parallel frequencies of 5–7 Hz; “priming”). Finally, patterned stimulation is most effective in inducing LTP in dentate gyrus when delivered at the peak of the dentate theta rhythm (Pavlidis et al. 1988), and a single burst well-timed within the theta cycle can produce significant synaptic potentiation or depression (Huerta and Lisman 1995). Together, these data suggest that “theta-burst” stimulation, that is, brief episodes of high-frequency stimulation applied in the appropriate temporal relationship to prior activity and to the ongoing theta rhythm, can reliably enhance synaptic efficacy in a brain area critical to the formation of certain types of memory. These observations suggest that theta bursts should be observable in real neural activity patterns associated with learning performance.

A study by Otto et al. (1991) found that all three of these characteristics of theta-burst patterned stimulation, together with optimal for hippocampal LTP induction, occur simultaneously and selectively during episodes of memory processing. Examination of the firing patterns of CA1 “complex spike” cells (Ranck 1973) in rats engaged in learning hippocampus-dependent spatial and olfactory tasks revealed that these cells discharged in high-frequency bursts, phase-locked to the positive peak of the dentate theta rhythm. Furthermore, these bursts were preceded by neural activity preferentially at intervals corresponding to the theta rhythm. Importantly, these theta burst patterns emerged only during significant behavioral events associated with likely periods of stimulus analysis, selection, or storage. Therefore, the optimal conditions for hippocampal LTP induction are present when animals actively engage hippocampal processing for putative mnemonic functions. These brief bursts may result in small and temporary adjustments of synaptic strengths across the network during learning that are later consolidated by coincident bursts that occur across the hippocampal population during “off-line” activities (Buzsaki and Chrobak 1995). It is certainly encouraging that these characteristics of natural activity patterns are so similar to those optimal for induction of LTP. But it remains unclear

whether the observed natural patterns actually produce changes in synaptic efficacy.

To address this question, a related approach is to employ these natural stimulation patterns as learning cues. These studies have demonstrated clear relationships between learning performance and synaptic responses to electrical stimulation used as the conditioning stimulus in learning situations. Roman and colleagues (1987, 1993) found that theta-burst patterned stimulation to the lateral olfactory tract (LOT) potentiates population EPSPs in the piriform cortex when the stimulation was employed as a discriminative cue substituting for an odor stimulus. Doyere and Laroche (1992) used high-frequency stimulation bursts in the perforant path as the cue in a conditioned emotional response paradigm, finding that the decay of burst-potentiated responses in the dentate gyrus predicted forgetting of the conditioned response. Given the recent Moser et al. (1993) findings, it is clear that findings now need to be confirmed with appropriate controls for the possibility that the effects are secondary to temperature changes and behavioral influences over hippocampal evoked potentials that could be associated selectively with the learned behaviors. However, if this approach is validated, it should be possible to examine whether depotentiation protocols would result in loss of memory performance (forgetting) for electrical conditioning stimuli.

A more fully natural approach involves studies that have examined whether transmission of sensory evoked responses are facilitated when the sensory stimuli are the cues for learning. Deadwyler and colleagues (1988) first examined this issue using a discrimination task where rats were required to distinguish between two pure tone stimuli. They found that auditory evoked field potentials in the dentate gyrus varied with the trial sequence such that the N1 component of the evoked potential was greatest following two S- trials and was smallest following two S+ trials. The size of the N1 accurately predicted the recent history across many trial sequences. In addition, these variations corresponded to trial sequence fluctuations in the magnitude of the dentate field EPSP to perforant path stimulation, showing a close parallel with the variations in the natural evoked potentials.

Recent observations from LeDoux and colleagues (Quirk et al. 1995; Rogan and LeDoux 1995) offer confirming evidence for a connection between the phenomena of LTP and enhanced sensory transmission in a different neural circuit that supports a different kind of memory. In this case the circuit under study is the pathway from the medial geniculate nucleus of the thalamus to the lateral amygdala nucleus that is part of the critical circuit for auditory fear conditioning. Rogan and LeDoux (1995) found that when high-frequency electrical stimulation of this pathway induces LTP, there is also an enhancement of amygdala synaptic responses to natural auditory stimulation. Furthermore, Quirk et al. (1995) have now shown that fear conditioning enhances short latency sensory responses of neurons in the amygdala. The magnitude, direction, and longevity of increases in auditory evoked synaptic potentials paralleled those parameters for electrically-induced synaptic potential, showing us that natural information processing can make use of the very cellular and molecular mechanisms set in place by conventional, artificially induced LTP. Correspondingly, the observation of increased neuronal sensory responses following conditioning shows us that, like

LTP, real learning can enhance information processing relevant to the task. Therefore, Deadwyler's and LeDoux's approaches take us beyond mere similarities between LTP and memory because they bring into contiguity the identical neural pathways and experimental procedures that define LTP and sensory processing in memory.

Finally, another approach pioneered recently by Wilson and McNaughton (1994) focuses on another likely consequence of enhanced functional connectivity in the hippocampal population following learning experiences. They found persistently increased cross-correlations among hippocampal neurons that were coactive during exploration of a novel environment. This approach, so far, lacks validation that the persistent correlations are functionally meaningful, but the findings are consistent with the possibility of LTP enhancing intrinsic or common afferent connections of neighboring hippocampal cells that encode related configurations of environmental cues. The main advantage of measuring hippocampal plasticity in terms of correlated firing is that both the learning situation and the physiological correlate are fully natural. It will be quite illuminating to determine what happens to hippocampal neuron firing properties under the influence of drugs that block LTP and in mutant mice without deficient hippocampal LTP. The strong prediction of the LTP-memory hypothesis would be that the cells should have normal prelearning firing patterns, typically reflecting the convergence of multimodal inputs (Eichenbaum 1996), but that plasticity, as reflected in altered cross-correlations or altered sensory transmission, will be lacking. A preliminary study showing that an NMDA-receptor blocker does not prevent the encoding of spatial information in hippocampal cells, but disrupts the development of a consistent spatial anchor (the place fields drift across repeated trials), offers evidence precisely in this direction (Austin et al. 1990). Such results contrasting normal information coding patterns versus blocked modifiability of the coded representations point us toward a potentially more decisive, and therefore more fruitful, way to link LTP and memory.

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