Heterosynaptic LTD and Depotentiation in the Medial Perforant Path of the Dentate Gyrus in the Freely Moving Rat

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Doyère, Valérie, Bolek Srebro, and Serge Laroche. Heterosynaptic LTD and depotentiation in the medial perforant path of the dentate gyrus in the freely moving rat, J. Neurophysiol. 77: 571–578, 1997. We examined the characteristics of heterosynaptic long-term depression (LTD) and depotentiation of previously established long-term potentiation (LTP) in the medial and lateral entorhinal afferents to the dentate gyrus in the awake rat. Rats were prepared for chronic recording of dentate gyrus evoked potentials to activation of the medial and lateral perforant paths. This study in awake rats confirms that heterosynaptic LTD can be induced at inactive medial perforant path synapses in conjunction with the induction of LTP produced by high-frequency stimulation of the lateral perforant path. This form of LTD was long lasting and reversible by tetanic stimulation delivered to the depressed pathway. In contrast, tetanic stimulation of the medial perforant path had only a small heterosynaptic effect on the lateral pathway, suggesting that the two input pathways to the dentate gyrus are not symmetrical in their ability to induce heterosynaptic LTD. We also examined the ability of high-frequency stimulation of one pathway to produce depotentiation of the other pathway. We found that when LTP was first induced in the medial perforant path, depotentiation was induced heterosynaptically by tetanization of the lateral pathway. Both newly established LTP (30 min) and LTP induced and saturated by repeated tetanic stimulation over several days can be depotentiated heterosynaptically. Moreover, depotentiation of the medial perforant path synapses was found to be linearly correlated with the magnitude of LTP induced in the lateral perforant path synapses, and subsequent tetanic stimulation of the depotentiated medial perforant path restored LTP to an extent that counterbalanced depotentiation. The saturation and repotentiation experiments provide clear support for the conclusion that the rapid reversal of LTP reflects true depotentiation of the medial input. Again, as with heterosynaptic LTD, tetanization of the medial perforant path had little effect on previously induced LTP in the lateral path. These results provide evidence that medial perforant path synapses can be depressed and depotentiated heterosynaptically. They suggest that in the intact rat synaptic changes in the afferents to the dentate gyrus from the lateral entorhinal cortex exert powerful control over ongoing or recent synaptic plasticity in the medial entorhinal afferents.

INTRODUCTION

The existence of rapidly induced, long-lasting and yet reversible changes in synaptic efficacy is an essential postulate in several models of the cellular basis for learning and memory. Activity-dependent long-term potentiation (LTP) of synaptic efficacy in neural networks is generally thought to form the basis for the neuronal changes that contribute to various forms of learning and memory (Bliss and Collingridge 1993; Davis et al. 1992; Doyère and Laroche 1992). It is also predicted that neural networks have the capacity to undergo a form of long-term depression (LTD) of synaptic transmission, or depotentiation of previously potentiated synapses (Bienenstock et al. 1982; Kohonen 1984; Morris and Willshaw 1989). Mechanisms leading to the down-regulation of synaptic weights are generally regarded as essential to prevent saturation of synaptic potentiation and increase the storage capacity of the network; they may also provide a cellular substrate for processes such as extinction, interference, forgetting, or retrieval failure. There is in fact experimental evidence to suggest that neural circuits in the dentate gyrus of the hippocampus (Doyère et al. 1995) and neocortex (Doyère et al. 1993; Roman et al. 1993) undergo synaptic depression in certain behavioral training conditions, yet the type of neuronal activation required to produce these effects remains underspecified.

In the hippocampus, two distinct forms of LTD have been described: homosynaptic LTD, a synapse-specific phenomenon that depends on presynaptic activity; and heterosynaptic LTD expressed at nonactivated neighboring synapses. The term depotentiation, or reversal of LTP, has been used to describe a rapid decrease in synaptic efficacy at potentiated synapses. In area CA1, homosynaptic LTD has been extensively studied using a stimulus protocol consisting of several hundred pulses at a frequency of 1–5 Hz to the Schaffer-commissural pathway, which was shown to produce input-specific LTD in the in vitro slice preparation (Dudek and Bear 1992, 1993; Mulkey and Malenka 1992). In several studies, depotentiation, but not LTD, was obtained in slices from mature animals (Fujii et al. 1991; O’Dell and Kandel 1994; Wagner and Alger 1995) or in vivo (Barrionuevo et al. 1980; Stäubli and Lynch 1990). In the intact adult animal, however, these effects have been difficult to reproduce. Recent studies in vivo have shown that prolonged low-frequency stimulation induces neither LTD nor depotentiation in area CA1 (Errington et al. 1995), whereas homosynaptic LTD was obtained by the use of repeated pairs of stimuli in both the anesthetized (Thiels et al. 1994) and freely moving adult rat (Doyère et al. 1996).

In the dentate gyrus, we found no evidence that LTD or depotentiation can be induced at any age in vivo with low-frequency stimulus trains (Errington et al. 1995) or series of paired stimuli (Doyère et al. 1996). In contrast, several studies have reported that heterosynaptic effects can be obtained in this region, for example, in the commissural system.
(Krug et al. 1985), the crossed perforant pathway (Levy and Steward 1979, 1983; White et al. 1990), or, ipsilaterally, in the medial and lateral entorhinal afferents (Abraham et al. 1985, 1994; Abraham and Goddard 1983; Christie and Abraham 1992a; Pang et al. 1993). Physiological studies thus gave reasons to suspect that the dentate gyrus may be more susceptible to heterosynaptic LTD, which may have important implications for the processing of information within hippocampal circuits. Controversies, however, have arisen in the research as to whether LTD at perforant path synapses can be reversed by heterosynaptic stimulation: Christie and Abraham (1992a) reported that depression of medial perforant path LTD can occur after high-frequency stimulation of the lateral perforant path in the anesthetized rat, whereas other studies suggested heterosynaptic depression is not observed if the test pathway has been previously potentiated (Abraham et al. 1985; Abraham and Goddard 1983).

In the present study we have investigated heterosynaptic interactions between medial and lateral perforant inputs to the dentate gyrus in the adult freely moving rat. In particular, we have examined the ability of these afferents to sustain heterosynaptic LTD and depotentiation of previously induced LTD. The study in awake rats confirms that a form of long-lasting heterosynaptic LTD is induced at inactive medial perforant path synapses in conjunction with the induction of LTD in the lateral perforant path. Tetanization of the medial perforant path, however, had little heterosynaptic effect on the lateral perforant pathway. We demonstrate that LTD of medial perforant path synapses can be depotentiated heterosynaptically in correlation with the induction of LTD in the lateral path. Furthermore, our results indicate that both newly established LTD and LTD saturated over several days can be depotentiated heterosynaptically.

**Methods**

**Animals and surgical procedures**

Thirty-six adult male Sprague-Dawley rats weighing 300–350 g at the time of surgery were used as subjects. Animals were housed individually with food and water ad libitum in a temperature-controlled room and on a 12-h light/dark cycle. Animals were anesthetized with sodium pentobarbitone (60 mg/kg ip, supplemented if necessary during surgery) and prepared for chronic recording. Recording electrodes consisted of two 62- to 100-μm wires inserted into a stainless steel microtube from which the recording electrode extended ≈1.5 mm. Two concentric bipolar electrodes (300-μm tip separation) were used to stimulate the lateral and medial perforant pathways. Coordinates for the recording electrodes were 4.2 mm posterior to Bregma and 2.5 mm lateral to the midline. Stimulating electrodes were placed ipsilaterally in the medial (MPP: 7.8 mm posterior, 4.2 mm lateral) and lateral (LPP: 8.2 mm posterior, 4.8–5.2 mm lateral) perforant paths. The depths of the recording and stimulating electrodes were adjusted to maximize the slope of the positive-going field excitatory postsynaptic potential (EPSP) evoked by stimulation of each pathway. For stimulation, this was generally ≈2.8 and ≈3.6 mm below the cortical surface for the medial and lateral electrodes, respectively. Stainless steel screws were positioned in the skull above the frontal and occipital cortices and served as reference and ground electrodes. All electrodes were connected to multichannel miniature sockets, fixed to the skull with dental acrylic.

**Experimental procedures**

Rats were allowed to recover from surgery in their home cages for at least 10 days and were then habituated to the recording chamber for 30 min each day for 3 days before the beginning of the experiments. Flexible recording and stimulating cables were passed through a multichannel rotating commutator at the top of the recording chamber. Recording always started 20 min after the rats were placed in the chamber. Field potentials evoked by test pulses (100–150 μs) delivered to the MPP and LPP were recorded through field effect transistors placed on the connecting sockets. Signals were amplified, filtered (band-pass 0.1 Hz to 3 kHz), digitized at 20 kHz, and stored on disk. The maximum slope of the medial and lateral EPSPs, and the area of the population spike were measured off-line.

Standard convergence tests were performed before the experiments to ensure that fibers activated by the MPP and LPP terminated on a common set of granule cells (Abraham and Goddard 1983; McNaughton and Barnes 1977). Test stimuli were delivered to the MPP and LPP, with the MPP stimulus following the LPP by 2–4 ms. Criterion for convergence was a population spike at least twice that of the arithmetic sum of the potentials evoked by stimulation of either pathway alone. Input/output (I/O) curves were also generated with the use of varying current intensities (20–800 μA) to determine the test intensity to be used in subsequent phases of the experiments for each pathway and individual rat. The levels were set to evoke an EPSP slope approximately one-half of its maximum. The criteria used to select animals with adequate separation of the MPP and LPP were based on 1) the characteristics of both lateral and medial evoked responses during I/O curves (McNaughton and Barnes 1977), which included a greater rise time and EPSP peak latency in the LPP response when compared with the MPP-mediated response, and a population spike falling on the descending phase of the lateral EPSP and on the rising phase of the medial EPSP; 2) post hoc tests where, at the end of the experiments, a small electrolytic lesion made by passing DC current through one electrode produced complete disappearance of the response elicited by stimulation of the lesioned pathway, without significantly affecting the response elicited by the other pathway; and 3) histological verification of lesions and electrode placement on brain sections stained with cresyl violet. The criteria for convergence and separation were met for 23 rats from which the results are reported here.

Field potentials were evoked alternately on the two pathways at 15-s intervals for 30 min each day. On days when tetanic stimulation was delivered, responses were also collected for 30–60 min after each tetanus. LTD was induced by the use of either a weak tetanic stimulus protocol (10 trains at a 1-min intertrain interval, each train consisting of 8 stimuli at 400 Hz), or a strong tetanic protocol used for saturating LTD (10 series of 7 × 400-Hz trains, 1-s intertrain interval, 1 min between each series). All trains were delivered at test intensity. The hippocampal electroencephalogram was monitored during all sessions to ensure the absence of electrically induced afterdischarges and that animals were in a still-alert state. Evoked responses were averaged in groups of four for each pathway, and values for EPSP slope and spike area were normalized for each animal with respect to the mean values obtained before the first tetanus (days 1–2). Effects were analyzed by paired two-tailed t-tests.

**Results**

**Heterosynaptic LTD in the medial perforant pathway**

In agreement with previous reports (Abraham et al. 1985; Abraham and Goddard 1983), high-frequency stimulation of the LPP consistently resulted in heterosynaptic depression.
HETEROSYNAPTIC LTD AND DEPOTENTIATION IN AWAKE RATS

FIG. 1. Heterosynaptic long-term depression (LTD) and depotentiation in the medial perforant pathway to the dentate gyrus of the awake rat. A: examples of responses to stimulation of the medial (left) and lateral (right) perforant path recorded before (dotted lines) and 30 min after (solid lines) the tetanus to the lateral perforant path (calibration: 2 mV, 2 ms). B: tetanic stimulation of the lateral perforant path (LPP; vertical dashed line) induced robust homosynaptic long-term potentiation (LTP; open circles) and heterosynaptic LTD of the medial perforant path (MPP) excitatory postsynaptic potential (EPSP; filled circles). Each point in this and subsequent graphs represents a group mean (±SE) of the averaged response to 4 test stimuli given at 30-s intervals on each pathway for a group of 6 animals. Maximal slope of the EPSP is expressed as a percent change relative to the baseline (30-min recording periods on days 1 and 2 before tetanization). C: 30 min after the induction of heterosynaptic LTD in the medial perforant path (as in B), tetanic stimulation of the MPP immediately restored the medial response to near control values (n = 6) but did not reverse LTP of the lateral path. D: tetanic stimulation of the MPP induced reliable LTP of the medial EPSP in a group of 5 animals. This procedure induced only a small heterosynaptic effect in the lateral path (open circles). LTP-inducing tetanization of the MPP delivered 30 min later, produced immediate and stable depotentiation of the medial EPSP (filled circles).

of synaptic transmission in the MPP (Fig. 1B). The decrease in the slope of the medial EPSP (−29.8 ± 4.2%, mean ± SE, 10–30 min after the LPP tetanus, P < 0.01, n = 6) occurred concurrently with potentiation of the lateral EPSP slope (45.3 ± 10.1%, P < 0.01). A mean depression of the medial EPSP slope of −16.6 ± 4.1% (P < 0.01, relative to the baseline, n = 6) was observed 24 h after tetanic stimulation of the LPP. The response, however, recovered to near-baseline values within 4 days (−0.3 ± 6.7%, day 6 in Fig. 1B), whereas the lateral EPSP slope remained significantly potentiated for at least 6 days (29.4 ± 4.2%; P < 0.01). The population spike of the medial field potential was also depressed after the LPP tetanus (−17.2 ± 4.5%, 50–70 min after lateral tetanus, P < 0.01, data not shown), recovering to baseline levels within 4 days.

Heterosynaptic LTD of the MPP response was replicated in a further group of animals (n = 6), where a decrease in the medial EPSP slope reached a mean value −26.6 ± 3.9% below baseline, 10–30 min after high-frequency stimulation of the LPP (Fig. 1C). Likewise, the magnitude of LTP elicited in the lateral pathway was comparable (43.9 ± 7.9%) with that in the first experiment. In this group, high-frequency stimulation delivered 30 min later to the depressed pathway restored the medial perforant path response to near baseline levels (−7.4 ± 7.1%, measured 10–30 min after the MPP tetanus, P > 0.05 compared with baseline, Fig. 1C). The population spike was slightly increased 10–30 min after the tetanus to the MPP (54.2 ± 21.9%), and then returned to near-baseline values after 24 h (data not shown). These results show that 1) depression of the medial EPSP produced by tetanic stimulation of the LPP is unlikely to be the result of a generalized deterioration of the preparation, and 2) heterosynaptic LTD of the MPP is reversible.

We examined the relationship between homosynaptic LTP and heterosynaptic LTD in both pathways. Although there was variability between subjects in the amount of LTP of the lateral pathway (range: 21.8–85.1%), and in LTD of the medial pathway (−13.7 to −46.2%), no significant correlation was found (r = 0.012, n = 12, ns), suggesting that there is no direct relationship between the magnitude of homosynaptic LTP and heterosynaptic LTD. It was also observed that tetanic stimulation of the MPP resulted in a small
but significant decrease in the potentiated lateral EPSP (−6.6 ± 1.8% relative to the potentiated level, measured 10–30 min after the MPP tetanus, \( P < 0.01 \), Fig. 1C). This was associated with a more rapid decay of LTP of the LPP, compared with the decay observed after tetanic stimulation of the LPP alone (see Fig. 1B), indicated by a lack of significant potentiation of the lateral EPSP slope 4 days after the LPP tetanus (9.9 ± 6.1%, \( P > 0.05 \)).

**Heterosynaptic depotentiation of the medial perforant path**

Five of the animals from the group presented in Fig. 1C also underwent the reverse experiment to examine the effect of high-frequency stimulation of the LPP delivered 30 min after the induction of LTP on the medial pathway. The order of the two protocols was randomized across animals, with at least 2 wk between them. None of the observed effects were significantly affected by the order of presentation (\( P > 0.05 \) in each case). In Fig. 1D, LTP was initially induced in the MPP by high-frequency stimulation (mean increase of 22.9 ± 2.1% of the slope of the medial EPSP; \( P < 0.05 \)). A small but significant heterosynaptic depression of the lateral EPSP occurred concurrently (−7.2 ± 1.6%, \( P < 0.05 \)). A tetanus then applied to the LPP produced both immediate potentiation of the lateral EPSP (34.4 ± 6.9%; \( P < 0.05 \)) and immediate decrease in the medial EPSP (Fig. 1D). The population spike of the medial field potential was not affected, remaining significantly potentiated for up to 24 h. Forty to 60 min after the LPP tetanus, the mean percentage change of the medial EPSP slope was −4.4 ± 2.6%. This was significantly less than the value observed after LTP (\( P < 0.05 \)), and not significantly different from the baseline before the MPP tetanus (\( P > 0.05 \)). The medial EPSP then remained at the baseline level for several days (Fig. 1D). We conclude from these results that high-frequency stimulation of the LPP can accomplish a near complete suppression of LTP of medial EPSP.

To test whether these changes were effectively due to heterosynaptic reversal of LTP, or depotentiation, another group of five animals was used in which LTP of the MPP was saturated by delivering the strong tetanic protocol (see METHODS), after which tetanic stimulation was applied to the LPP, and LTP was reinduced (Fig. 2B). Strong tetanic stimulation of the MPP induced rapid saturation of LTP of the medial EPSP (36.5 ± 1.9%, compared with 43.1 ± 5.5% with repetition of the same protocol in Fig. 2D, \( P > 0.05 \)), and of the population spike (data not shown). We observed that even with this strong protocol, there was only minimal heterosynaptic depression of the lateral EPSP (only 3 out of 8 rats from experiments illustrated in Fig. 2, B and D, showed small depression with an average of −8.7%). A strong tetanus applied to the lateral perforant path then resulted in almost complete suppression of LTP of the medial EPSP (Fig. 2B). The decrease in the response represented suppression of 77.2 ± 13.8% of LTP, and values of the EPSP were not significantly different from the baseline preceding the first tetanus (7.9 ± 5.2%, \( P > 0.05 \)). As shown in Fig. 2B, a strong tetanus applied 30 min later to the MPP invariably reestablished LTP of the medial EPSP to a level (27.9 ± 4.4%) that was close to that obtained before high-frequency stimulation of the LPP. Under similar conditions we tested the effect of weak tetanic stimulation of the LPP after saturation of LTP on the MPP (\( n = 3 \)). In this case, there was only small depotentiation of the medial EPSP, which remained significantly above baseline (24.3 ± 8.8%, \( P < 0.05 \), data not shown), although this was less than the levels of both previously saturated LTP (40.9 ± 5.8%), and reestablished LTP (39.3 ± 7.4%). In all cases, there was no significant effect of the LPP tetanus on the area of the population spike.

We then carried out experiments to examine the efficacy of the depotentiating stimulus at a longer interval after the induction of LTP. In one group (\( n = 3 \)), LTP of the MPP was first saturated by the use of repeated strong tetanic stimulation, applied twice each day for 4 days. The magnitude of LTP obtained on the first day of induction (43.1 ± 5.5%), and that observed 24 h after the last day of tetanization (39.7 ± 15.7%) are illustrated on Fig. 2D. A strong tetanus applied to the LPP, 24 h after the last MPP tetanus, induced complete depotentiation of the medial EPSP, and LTP was again reestablished upon high-frequency stimulation of the MPP. The slope of the medial EPSP after the depotentiating stimulus was significantly below the potentiated level (\( P < 0.01 \)), but not significantly different from the pretetanus baseline (\( P > 0.05 \)). Thus the ability of the LPP tetanus to depotentiate the MPP-evoked response does not require a short time lag between the two tetani, and depotentiation can be almost entirely accomplished, after a delay of at least 24 h. Animals from the experiment illustrated in Fig. 2B were next used to examine the depotentiation-repotentiation sequence with repeated triplets of MPP-LPP-MPP tetani over 4 days. The results are illustrated in Fig. 2C. As expected, large LTP was induced on day 1, yet only small increments were observed on each of the following days (reflecting only that part of LTP that decays within 24 h). The analysis confirmed that a tetanus to the LPP on day 1 can produce almost complete depotentiation, whereas the MPP tetanus can repotentiate the response to a level that nearly compensates for depotentiation. The difference in the amount of repotentiation (stippled bar), compared with the level of LTP observed after the first MPP tetanus (open bar; see also Fig. 2, B and C), was ascribed to a small heterosynaptic depression of the MPP after the LPP tetanus (e.g., Fig. 1D). On day 2, the LPP tetanus induced depotentiation (filled bar) that was significantly greater (\( P < 0.01 \)) than the newly induced LTP (open bar), again suggesting at least partial depotentiation of a part of the “old” LTP induced at the end of the previous day. This effect, however, is not observed on the following days, suggesting a decrease in the efficacy of the LPP tetanus to depotentiate an old (>1 day) LTP, while its ability to depotentiate a recently reinduced LTP remains.

The relationship between LTP of the LPP and heterosynaptic depotentiation of the MPP was further analyzed in those rats that contributed to the saturation experiments. We found that the magnitude of depotentiation of the MPP was linearly correlated with the amount of LTP induced in the LPP (\( r = 0.763, n = 11, P < 0.005 \), Fig. 3A), whereas no correlation was found with the magnitude of LTP first induced in the MPP (\( r = 0.190, n = 11, \text{ns} \)). We conclude that the efficacy of the depotentiating stimulus is for a large part determined by its propensity to induce LTP of the LPP, and that this effect does not depend on the actual level of
LTP of the MPP. We also found that repotentiation of the medial EPSP was linearly correlated with the amount of depotentiation induced by the LPP tetanus ($r = 0.818, n = 11, P < 0.005$, Fig. 3B), suggesting that almost all that is depotentiated can be repotentiated.

**DISCUSSION**

The two main findings in these experiments are 1) the induction of long-lasting, yet reversible, heterosynaptic LTD in the medial perforant path input to the dentate gyrus in the awake rat in conjunction with the induction of LTP in the lateral input; and 2) the ability of the medial input to be depotentiated heterosynaptically in relation to potentiation induced in the lateral input. We report, furthermore, that depotentiation of the medial input is correlated linearly with the amplitude of LTP in the convergent pathway and that tetanic stimulation of the depotentiated pathway restores LTP.

The present experiment confirms in the awake rat previous reports of heterosynaptic LTD in the entorhinal afferents to the dentate gyrus (Abraham et al. 1985; Abraham and Goddard 1983). In the medial perforant pathway, heterosynaptic LTD was as readily obtained in the present experiment in the freely moving rat as previously reported in the anesthetized rat (Abraham et al. 1985; Abraham and Goddard 1983). We confirm that this form of LTD is long lasting (Abraham et al. 1994) and show in the awake animal that...
and awake rat (Abraham et al. 1994) where heterosynaptic LTD in the lateral path was more robust than in our study. Although the stimulus intensity was kept constant in the present experiment, the intensity for tetanic stimulation of the medial pathway was increased almost twofold in the other studies. Increasing the intensity may enlarge the portion of the dendritic field receiving tetanized fibers, thereby increasing the likelihood that the test pathway spatially overlaps the dendritic field where homosynaptic LTP is produced, a procedure that has been shown to favor the induction of heterosynaptic LTD (White et al. 1988, 1990). An alternative hypothesis is that the weaker ability of the lateral perforant path to sustain LTD and de potentiation in these experiments may reflect masking of the effects by concurrent potentiation of a medial component in the response. Although it remains possible that stimulation of the lateral perforant path electrode also activated some medial perforant path fibers, this is unlikely to explain the observed asymmetry between the two pathways, because the lesion test performed after the induction of LTP (see METHODS) suggests that medial perforant path fibers, if any, would not have been activated and potentiated when a tetanus is delivered through the medial perforant path electrode.

The other finding of the present study is that LTP in the medial perforant pathway can be de potentiated by high-frequency tetanic stimulation of the lateral perforant pathway. This contrasts with studies of Abraham and Goddard (1983) and Abraham et al. (1985), but confirms and extends to the awake rat more recent observation of a reversibility of medial perforant path LTP (Christie and Abraham 1992a). It is interesting to note that high-frequency stimulation of the lateral perforant path had little effect on the population spike of the medial perforant path evoked potential. Neither LTD nor de potentiation of the population spike were reliably obtained. These results confirm and extend to de potentiation previous observations in the anesthetized rat and suggests that EPSP-spike (E-S) potentiation may at least partially compensate for depression of the EPSP (Abraham et al. 1985).

Four other aspects of this study have important implications for functional and computational properties of synaptic plasticity in the dentate gyrus. First, the saturation and repotentiation experiments provide clear support for the conclusion that the rapid reversal of LTP of the EPSP reflects true de potentiation of the medial input. Otherwise, if the decrease in the response was due to the induction of LTD at other synapses, superimposed on LTP, repotentiation would not have been observed. Moreover, the correlation analysis showed that the magnitude of repotentiation matched closely, and in fact almost compensated for de potentiation of the EPSP (Abraham and Goddard 1983).

It is reversible by tetanic stimulation of the depressed pathway. Our results suggest, however, that the medial and lateral perforant paths are not symmetrical in this respect. In the awake rat, the lateral perforant pathway clearly appeared to be less susceptible to heterosynaptic LTD than the medial pathway. This differs from results obtained in the anesthetized (Abraham and Goddard 1983; Christie and Abraham 1992a,b; Christie et al. 1995) and awake rat (Abraham et al. 1994) where heterosynaptic LTD in the lateral path was more robust than in our study. Although the stimulus intensity was kept constant in the present experiment, the intensity for tetanic stimulation of the medial pathway was increased almost twofold in the other studies. Increasing the intensity may enlarge the portion of the dendritic field receiving tetanized fibers, thereby increasing the likelihood that the test pathway spatially overlaps the dendritic field where homosynaptic LTP is produced, a procedure that has been shown to favor the induction of heterosynaptic LTD (White et al. 1988, 1990). An alternative hypothesis is that the weaker ability of the lateral perforant path to sustain LTD and de potentiation in these experiments may reflect masking of the effects by concurrent potentiation of a medial component in the response. Although it remains possible that stimulation of the lateral perforant path electrode also activated some medial perforant path fibers, this is unlikely to explain the observed asymmetry between the two pathways, because the lesion test performed after the induction of LTP (see METHODS) suggests that medial perforant path fibers, if any, would not have been activated and potentiated when a tetanus is delivered through the medial perforant path electrode.

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It is reversible by tetanic stimulation of the depressed pathway. Our results suggest, however, that the medial and lateral perforant paths are not symmetrical in this respect. In the awake rat, the lateral perforant pathway clearly appeared to be less susceptible to heterosynaptic LTD than the medial pathway. This differs from results obtained in the anesthetized (Abraham and Goddard 1983; Christie and Abraham 1992a,b; Christie et al. 1995) and awake rat (Abraham et al. 1994) where heterosynaptic LTD in the lateral path was more robust than in our study. Although the stimulus intensity was kept constant in the present experiment, the intensity for tetanic stimulation of the medial pathway was increased almost twofold in the other studies. Increasing the intensity may enlarge the portion of the dendritic field receiving tetanized fibers, thereby increasing the likelihood that the test pathway spatially overlaps the dendritic field where homosynaptic LTP is produced, a procedure that has been shown to favor the induction of heterosynaptic LTD (White et al. 1988, 1990). An alternative hypothesis is that the weaker ability of the lateral perforant path to sustain LTD and de potentiation in these experiments may reflect masking of the effects by concurrent potentiation of a medial component in the response. Although it remains possible that stimulation of the lateral perforant path electrode also activated some medial perforant path fibers, this is unlikely to explain the observed asymmetry between the two pathways, because the lesion test performed after the induction of LTP (see METHODS) suggests that medial perforant path fibers, if any, would not have been activated and potentiated when a tetanus is delivered through the medial perforant path electrode.

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Four other aspects of this study have important implications for functional and computational properties of synaptic plasticity in the dentate gyrus. First, the saturation and repotentiation experiments provide clear support for the conclusion that the rapid reversal of LTP of the EPSP reflects true de potentiation of the medial input. Otherwise, if the decrease in the response was due to the induction of LTD at other synapses, superimposed on LTP, repotentiation would not have been observed. Moreover, the correlation analysis showed that the magnitude of repotentiation matched closely, and in fact almost compensated for de potentiation of the EPSP (Abraham and Goddard 1983). No such correlation was observed with heterosynaptic LTD in the ‘‘naive’’ (nonpotentiated) pathway. Although this may indicate that the two effects involve different mechanisms, as has been argued to occur in CA1 (Wagner and Alger 1995), it is also entirely possible that what we call naive synapses have developed some form of potentiation during the animal’s lifetime and that the correla-
tion can only be observed after a saturation procedure has brought LTP to comparable levels across animals. Finally, our data suggest that LTP of the lateral perforant path can induce LTD of the medial perforant path, but if the medial path is first potentiated, only depotentiation occurs. Studies examining the effect of tetanization of the lateral perforant path on a depotentiated medial response will provide further evidence for or against the involvement of separate mechanisms. In any event, the correlation between LTP in the lateral pathway and depotentiation of the medial pathway places constraints on the heterosynaptic interactions between the two inputs, where potentiation of one subset of synapses would be expected to depotentiate neighboring inputs to a quantitatively similar extent.

Third, our results suggest that if there is a temporal window during which LTP of the medial perforant path can be depotentiated, this window is probably not narrow because we were able to induce depotentiation 1 day after LTP had been saturated by repeated tetanic stimulation over several days. This contrasts with what has been suggested to occur in area CA1 where depotentiation, induced homosynaptically, can only be obtained within a relatively short temporal window (Fuji et al. 1991; Stäubli and Chun 1996). Thus depotentiation in the dentate gyrus can occur outside of the short temporal window that appears to exist in the CA1 region. Although further experiments are needed to determine whether there is a time point after which LTP of the medial perforant path becomes resistant to reversal, this result suggests that depotentiation produced by heterosynaptic activation is unlikely to involve the reversal of some of the cellular/molecular mechanisms that mediate the expression of LTP in its first phases. Finally, we found that the two perforant pathways are not symmetrical with regard to both heterosynaptic LTD and depotentiation. Plasticity in the medial perforant path can be rapidly regulated because this pathway has the ability to express both heterosynaptic LTD and depotentiation. In contrast, the lateral perforant pathway expresses LTP as the medial pathway, yet neither depotentiation nor LTD could be reliably induced by heterosynaptic stimulation.

In summary, the results provide evidence that the induction of synaptic potentiation in the lateral perforant pathway produces LTD heterosynaptically and can reverse previously induced changes in synaptic efficacy of the medial perforant path synapses. The physiological implication is that activity carried along the lateral entorhinal afferents to the dentate gyrus during the encoding of information within hippocampal networks is likely to exert a powerful control over ongoing or recent synaptic plasticity of the medial entorhinal afferents, whereas synaptic changes at lateral perforant path synapses will be less susceptible to modulation or resetting by synaptic changes occurring on the medial perforant path synapses.

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