“Heterosynaptic” LTD in the Dentate Gyrus of Anesthetized Rat Requires Homosynaptic Activity

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Abraham WC, Logan B, Wolff A, Benuskova L. “Heterosynaptic” LTD in the dentate gyrus of anesthetized rat requires homosynaptic activity. J Neurophysiol 98: 1048–1051, 2007. First published May 30, 2007; doi:10.1152/jn.00250.2007. Heterosynaptic long-term depression (LTD) is conventionally defined as occurring at synapses that are inactive during a time when neighboring synapses are activated by high-frequency stimulation. A new model that combines computational properties of both the Bienenstock, Cooper and Munro model and spike timing-dependent plasticity, however, suggests that such LTD actually may require presynaptic activity in the depressed pathway. We tested experimentally whether presynaptic activity is in fact necessary for previously described heterosynaptic LTD in lateral perforant path synapses in the dentate gyrus of urethane-anesthetized rats. As predicted by the model, procaine infusion into the lateral path fibers, sufficient to transiently block neural activity in this pathway, prevented the induction of LTD in the lateral path following medial path high-frequency stimulation. These data indicate that the previously described heterosynaptic LTD in the dentate gyrus in vivo is actually a form of homosynaptic LTD, requiring presynaptic activity in the depressed pathway.

INTRODUCTION

Traditionally, long-term depression (LTD) has been classified as being either homo- or heterosynaptic in nature (Bear and Abraham 1996). Homosynaptic LTD (hom-LTD) refers to depression at the same synapses as those stimulated to induce the LTD effect. In contrast, heterosynaptic LTD (het-LTD) refers to depression at synapses neighboring the activated ones but not directly activated themselves. In this latter case, the stimulated synapses typically exhibit homosynaptic LTD simultaneously with the het-LTD, although it is not clear that this is a requirement for het-LTD induction. In the hippocampus, hom-LTD has been observed in all excitatory pathways tested. Het-LTD has been more elusive, with the bulk of reports arising from in vivo studies of perforant path synapses in the dentate gyrus (Abraham and Goddard 1983; Doyere et al. 1997; Levy and Steward 1979). Intriguingly, het-LTD is difficult to obtain in dentate gyrus synapses in vitro (Hanse and Gustafsson 1992), whereas hom-LTD is more readily observed (Wu et al. 2001).

One difference between in vivo and in vitro dentate gyrus preparations may be the degree of resting activity in the presynaptic axons. Typically resting activity is low in the slice preparation and certainly in the dentate gyrus the perforant path axons are expected to be completely quiescent as their cell bodies of origin in the entorhinal cortex have been cut off during slice preparation. In contrast, entorhinal cortical neurons afferent to the dentate gyrus exhibit resting activity on the order of 2–8 Hz in the anesthetized preparation (Dickson et al. 1994; Gloveli et al. 1997). Could such ongoing activity contribute to het-LTD induction in vivo? In a recent computational model of dentate synaptic plasticity that merges principles of the Bienenstock, Cooper, and Munro (BCM) model (Bienenstock et al. 1982) and spike timing-dependent plasticity, we observed that simulated het-LTD in the lateral perforant path synapses could be readily induced when the medial perforant path was given LTP-inducing stimulation (Benuskova and Abraham 2007). However, induction of such apparent het-LTD may in fact have required activity in the depressed pathway during medial path high-frequency stimulation (HFS) because this model incorporates a parameter for ongoing synaptic activity in the lateral path at a rate of 8 Hz as observed experimentally (Frank et al. 2001). The results from this modeling prompted us to address more carefully the role of resting activity in het-LTD through experimental hypothesis testing and further modeling. Our results indicate that apparent het-LTD in vivo is in fact a form of hom-LTD, dependent on activity in the depressed pathway.

Adult male Sprague-Dawley rats (2–4 mo) were anesthetized with urethan (1.5 g/kg ip) and prepared for stereotaxic implantation of medial and lateral path stimulation electrodes plus an extracellular field potential recording electrode in the dentate hilus, as previously described (Christie and Abraham 1992) and as approved by the University of Otago Animal Ethics Committee. The lateral path stimulating electrode was glued to a 30-gauge stainless steel cannula such that it projected ~0.5 mm below the cannula. The cannula was attached via polyethylene tubing to a syringe pump (Harvard Apparatus, Holliston, MA) for microinjection of either procaine (200 mg/ml) or phosphate-buffered saline (PBS) vehicle. The medial and lateral path electrode positions were adjusted to maximize evoked field potentials with the electrophysiological signatures of each pathway, including wave shape and paired-pulse responses, as previously described (Abraham and Goddard 1983; Abraham et al. 2001).

Low-frequency baseline stimulation (150–600 μA, 150-μs pulse duration) alternated between the two perforant pathways at 15-s intervals. When the responses were stable for 30 min, either PBS or procaine (0.25 μl) was injected into the lateral...
path over a 2.5-min period. HFS, consisting of 50 trains (400 Hz, 25 ms, 250-μs pulse duration) given in sets of five trains at 0.1 Hz (1 min between sets), was given to the medial path 5 min after solution injection. Test shocks at the baseline intensity and frequency were resumed for a further 60-min recording period. The slope of the field excitatory postsynaptic potentials (fEPSPs) was measured for both the medial and lateral path responses and expressed as a percentage change from the average baseline value prior to injection. Statistical comparisons between groups were made by Student’s t-test, with a significance level set at 0.05. All data are expressed as means ± SE.

For modeling heterosynaptic plasticity in the dentate gyrus, we used the computational model described in Benuskova and Abraham (2007), in which one model neuron represents the whole population of experimentally tested granule cells. The model neuron is the Izhikevich spiking neuron (Izhikevich 2003) with two input pathways, the lateral and medial perforant paths. Each input is characterized by a certain number of input fibers engaged by stimulation and by the synaptic weight of each fiber. Synapses modify according to a spike-timing-dependent plasticity (STDP) rule. We made the size of STDP windows for LTP and LTD changeable as a function of the previous average of postsynaptic activity of the model granule cell according to the relation proposed for the BCM moving LTD/LTP threshold (Bienenstock et al. 1982). Less average activity in the past leads to a bigger timing window for potentiation and a smaller window for depression, and vice versa.

In the model’s control condition, where simulated ongoing activity was present at both input pathways, medial HFS led to medial path LTP and lateral path het-LTD (Fig. 1, A and B), similar to that observed experimentally (Abraham et al. 2001). The requirement for presynaptic activity to generate LTD in the lateral path following medial path HFS was tested by setting the lateral path resting and evoked activity parameters to zero for a 5-min period prior to the simulated HFS and for the subsequent testing period. As can be seen in Fig. 1A, this parameter change had no influence on the induction of LTP in the medial path but completely prevented the development of LTD in the lateral path (Fig. 1B) as detected by monitoring the total synaptic weights corresponding to the medial and lateral paths, respectively. Thus in the model, induction of apparent “heterosynaptic” LTD in the lateral path actually is dependent on activity in that pathway.

To experimentally test the need for presynaptic activity in the lateral path to induce LTD in vivo, the local anesthetic procaine was injected into the lateral path component of the angular bundle through a cannula attached to the stimulating electrode. The injection was considered to have successfully blocked lateral path presynaptic activity selectively if the fEPSP response to lateral path test pulse stimulation was reduced by ≥85%, whereas the medial path response was not reduced at all. HFS was given to the medial path during maximal inhibition of the lateral path response (Fig. 2). As expected, procaine delivery had no effect on the degree of LTP elicited in the medial path measured 60-min post-HFS compared with saline vehicle-treated controls (37 ± 5%, n = 7 vs. 37 ± 4%, n = 7, respectively, n.s.; Fig. 2A). In contrast, the degree of lateral path response suppression in the same animals at this time point was reduced in the procaine-treated group (−10 ± 6%, n = 7) compared with the control group (−24 ± 3%, n = 7; P < 0.05; Fig. 2B). When a second medial path HFS was delivered, the control group showed no further lateral path LTD. Likewise, the second HFS in the procaine group generated no LTD; rather, the lateral path response continued to return toward baseline (−5 ± 8%, n = 6).

The residual response suppression noted in the procaine-treated group was not a reduced degree of LTD but rather a result of the slow washout of procaine because a third group of animals given procaine but no HFS showed a similar degree of slow recovery from the response suppression (−11 ± 3%, n = 6; Fig. 3, A, B, and D). Thus procaine during the HFS appeared to completely block het-LTD. What was still uncertain was whether resting activity was sufficient to preserve the het-LTD or whether the stimulus-evoked activity also was necessary because both would be blocked by procaine. To test this, we simply stopped stimulating the lateral path during and for 40 min after medial path HFS, a procedure that should have left relatively undisturbed the resting activity in the lateral path, although this could not be directly verified in the present experiment. In the absence of procaine, stopping lateral path
stimulation did not prevent LTD from occurring (\(-17 \pm 5\%, n = 6\); Fig. 3, C and D), but as this was slightly less than the control level of LTD, it remains possible that evoked activity contributed to a small portion of the full LTD in control animals.

One intriguing finding was that a second HFS given to the original procaine group after washout failed to elicit lateral path LTD (Fig. 2B). We considered that this reflected either a residual effect of the procaine itself or else a persistent effect of the temporary loss of lateral path resting activity. However, neither interpretation was correct as the procaine control group that did not receive medial path HFS until 60 min after washout did show normal LTD after receiving an HFS (\(-35 \pm 7\%, n = 4\); Fig. 3B). This suggests that the continued lack of LTD in the original procaine group was a metaplastic effect of the first HFS, which prevented LTD induction 60 min later in much the same way as it prevented further LTP induction (Fig. 2A) (Frey et al. 1995). An alternative view to the metaplasticity explanation is that LTD is conditional on generation of LTP in the stimulated pathway (Doyere et al. 1997), perhaps as a method of normalizing overall synaptic input to the postsynaptic neurons. However, we currently believe this interpretation to be less likely as LTP and LTD are not generally tightly coupled in the hippocampus given the many examples of LTP (e.g., present experiment) and LTD (many studies of homosynaptic LTD) being induced in isolation.

Taken together, the findings from both the computational modeling and the electrophysiological experimentation strongly support the view that so-called “het-LTD” in the dentate gyrus in vivo actually is a form of hom-LTD that requires presynaptic activity in the depressed pathway during the period of LTD induction. In the case of the modeling, this is not surprising because the model does not include a parameter that would permit LTD induction in the absence of presynaptic activity. However the model was instructive because it demonstrated that resting activity in one pathway is in principle sufficient to induce LTD when local conditions are altered by the HFS in a separate pathway. In the model, medial path HFS generates a period of time when the lateral path activity is decorrelated with granule cell firing and thus more.
susceptible to spike-timing-dependent LTD. The experimental work confirmed that resting activity in the to-be-depressed synapses is necessary for LTD induction as block of resting activity in the lateral path by procaine (gauged by the loss of stimulus-evoked responses) was sufficient to prevent LTD. In contrast, procaine delivery had no effect on medial path LTP, nor on the metaplastic inhibition of LTP and LTD induction by a second HFS. One cautionary note to these interpretations is that the present experiments were conducted in urethane-anesthetized animals. We predict that similar mechanisms account for het-LTD in awake animals, but this remains to be tested.

The presence of ongoing presynaptic activity in vivo raises the question of why it does not cause hom-LTD under these resting conditions and therefore occlude further depression as induced experimentally. In the model, as noted in the preceding text, the modification threshold has settled at a point where LTD and LTP are balanced and no net change occurs (Benuskova and Abraham 2007). HFS leads to desynchronization of medial and lateral path presynaptic activity and therefore reduced co-occurrence of presynaptic activity and postsynaptic spiking during the STDP window for potentiation. Net LTD thus occurs. This may explain the pattern of results in vivo, but other interpretations are also possible. For example, there may be a modifiable threshold for LTD (Artola and Singer 1993) that is driven to the right by spontaneous activity until such activity is incapable of inducing LTD. Hom-LTD in this case would require more synchronized and therefore depolarizing presynaptic activity than occurs spontaneously to be induced (see also Kerr and Abraham 1995). To cross this LTD threshold, it may take the medial path HFS to drive the threshold transiently to the left and thereby permit basal activity to elicit LTD. Alternatively, it is conceivable that lateral path activity is increased transiently through polysynaptic activation of this pathway during medial path HFS.

The requirement for presynaptic activity to induce “het-LTD” helps explain why it has been easier to observe in the dentate gyrus of intact animals than in the dentate gyrus slice preparation for which there have been no reports of het-LTD to our knowledge. This mechanism also appears to contribute to het-LTD described in polysynaptic visual pathways of anesthetized kittens (Tamura et al. 1992). Het-LTD has been reported, however, in hippocampal CA1 slices, particularly under conditions of very strong stimulation and postsynaptic depolarization (Abraham and Wickens 1991; Scanziani et al. 1996). It may be that under these conditions there is a very large shift in the modification threshold such that very low levels of resting activity in CA3 pyramidal cells, or even spontaneous release of transmitter at the Schaffer collateral terminals, is sufficient to elicit the LTD. Alternatively, under these conditions a true het-LTD at nonactive synapses may be generated through sufficient calcium mobilization postsynaptically, as theorized by Artola and Singer (1993) or else a diffusible signal for LTD induction is released by neighboring cells (Scanziani et al. 1996).

The LTD evoked in the present experimental study appears to be a hybrid form of LTD akin to previously described associative LTD (Christie and Abraham 1992; Debanne et al. 1994; Stanton and Sejnowski 1989). Here presynaptic activity is normally insufficient to cause plasticity, but it has the capability to do so when conditions are associatively altered by activity in a second pathway, in this case medial path HFS. In our model, the key alteration induced by the HFS is a decorrelation of lateral path presynaptic activity and granule cell postsynaptic activity (Benuskova and Abraham 2007). Regardless of the actual mechanism, these findings point to a complex dynamism of the plasticity properties of perforant path synapses that is a function of activity in all the afferent pathways.

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R E F E R E N C E S


