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Initial synaptic efficacy influences induction and expression of long-term changes in transmission

(long-term depression/inhibition/Mauthner cell/electrotonic synapses)

XIAN-DA YANG AND DONALD S. FABER

Neurobiology Laboratory, Department of Physiology, School of Medicine, State University of New York at Buffalo, Buffalo, NY 14214

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ABSTRACT **Long-term depression (LTD) of glutamatergic and electrotonic transmission can be induced at mixed synapses between eighth nerve fibers and the goldfish Mauthner (M) cell *in vivo*, by pairing weak presynaptic tetani with postsynaptic inhibition. This LTD can be reversed by stronger tetani that produce long-term potentiation (LTP). Moreover, the depression is more likely to occur and tends to last longer when the initial synaptic efficacy is high—that is, if the synaptic strength is first potentiated. In addition, when synaptic efficacy is initially elevated, a weak tetanization that usually results in a gradually developing potentiation instead produces no change in chemical transmission and even a depression of electrotonic coupling. Thus, the modifications in synaptic transmission caused by a certain tetanizing protocol depend upon the history of synaptic efficacy. This last concept provides an experimental basis for theoretical models concerned with pre- and postsynaptic contributions to the regulation of synaptic plasticity.**

Two opposing forms of activity-dependent modifications of synaptic transmission that are considered to be bases for neural plasticity are long-term potentiation (LTP) (1–4) and long-term depression (LTD) (5–8). One issue of concern has been the identification of conditions which, for the same synaptic connection, differentially favor the induction of one or the other of these alterations. Recently, it was shown that, in visual cortical slices, presynaptic tetani produce either homosynaptic LTD or LTP, depending upon the global level of disinhibition produced pharmacologically or upon the magnitude of postsynaptic depolarization by the tetanus (8). It was also suggested that there are depolarization thresholds for both phenomena, with that for homosynaptic LTD being closer to the resting potential than that for LTP. We provide evidence here for a concept not considered previously—namely, that the thresholds for the two phenomena might vary with the initial level of synaptic efficacy of the involved connections. Specifically, while studying homosynaptic LTD of both electrotonic coupling and chemical transmission at mixed synapses onto an identified reticulospinal neuron, we found that the amplitude, duration, and sign of long-term changes in synaptic transmission produced by a certain tetanizing protocol depended upon the pretetanization level of efficacy. In addition, it is shown that postsynaptic inhibition is an important factor in induction of LTD *in vivo*.

MATERIALS AND METHODS

LTP and LTD have been studied at the monosynaptic connection between eighth nerve fibers and the Mauthner (M) cell in goldfish (*Carassius auratus*). As shown in Fig. 1*A*, single afferents have both gap junctions and chemical synapses on the M cell's lateral dendrite. Standard surgical procedures were used, and intracellular recordings of the eighth nerve responses were obtained *in vivo* from the lateral dendrite about 200 to 250 μm from the M cell soma, generally with a KCl (2.5 M)-containing microelectrode of 7–15 MΩ resistance. In addition, the M cell and its recurrent inhibitory network were activated antidromically through an electrode on the spinal cord (10). EPSPs evoked by stimulation of the contralateral optic tectum (11), which projects to the ventral dendrite of the M cell, were also recorded in some instances. The intradendritic resting membrane potential was in the range of −75 to −88 mV and remained stable throughout each experiment, as did the amplitude of the antidromic action potential, which is an indicator of M cell input resistance (12). Responses were measured, from prestimulation baseline to peak, after averaging sets of 15 or more traces. The eighth nerve test stimulus strength was such that the range of postsynaptic coupling potential amplitudes was about 15–25 mV and the chemical EPSPs were about 5 mV. With these recording conditions, Cl^- loading of the M cell did not occur and inhibitory responses were not associated with significant membrane potential changes, since the Cl^- equilibrium potential equals the resting membrane potential (10, 12).

We previously showed that repeated brief strong tetani of the eighth nerve, with the M cell firing an action potential at least once each tetanus, were more effective in producing LTP of both the coupling potential and the chemical EPSP than a weaker tetanization that did not fire the M cell (13). In the present study, two additional tetanizing paradigms were used: (*i*) a weak tetanus where the conditioning and test stimulus strengths were similar and below the threshold for M cell spike initiation, and (*ii*) the weak tetanus paired with one spinal cord stimulus to evoke both an antidromic impulse and the feedback inhibition (Fig. 1*A*). Generally, the weak tetanus consisted of three to five eighth nerve stimuli at 500 Hz repeated every 2 s for 6–8 min, whether it was applied alone or in conjunction with the antidromic stimulus. In the case of the potentiating paradigm, the tetanus consisted of three to five stronger stimuli, repeated as before for 2–6 min.

RESULTS

When the weak tetanus was paired with a spinal cord stimulus, we observed relatively long-lasting depressions in six of nine experiments (Fig. 1*B*), with no effect in the other three. The depression was specific to the tetanized pathway, as the EPSP evoked via the optic tectum was either unchanged or slightly enhanced (Fig. 1*C*). The depression observed 12 min after the tetanus ranged from 13% to 41% (n = 6) for the coupling potential (mean = 26%), and from 13% to 70% (n = 6) for the chemical EPSP (mean = 34%) when the amplitudes of the responses were expressed as percentages of the baseline level before the tetanus. In four of the six experiments, the depression was transient, as the responses

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Abbreviations: LTP, long-term potentiation; LTD, long-term depression; M cell, Mauthner cell; EPSP, excitatory postsynaptic potential.

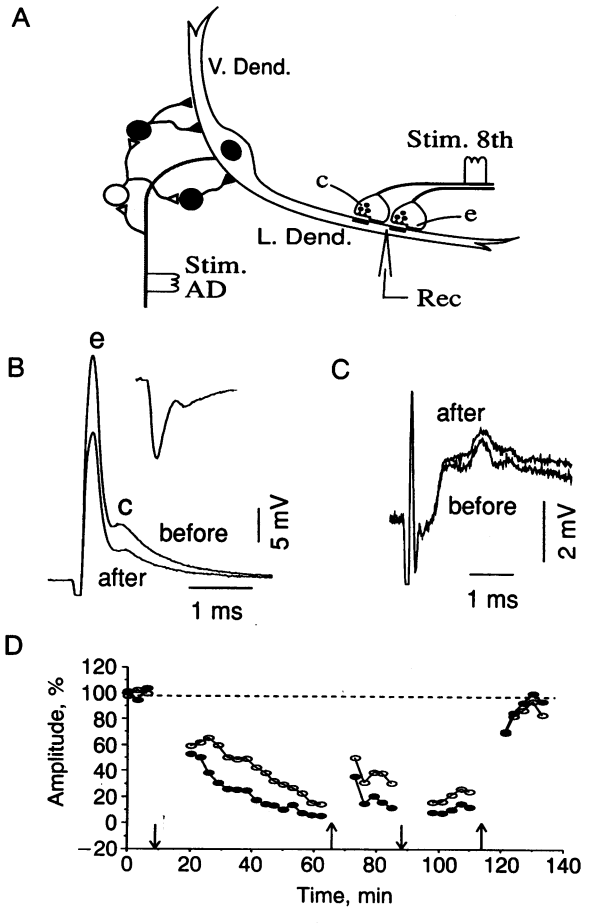

FIG. 1. LTD is produced by pairing subthreshold tetanization with inhibition. (*A*) Diagram of the experimental arrangement. V. Dend. and L. Dend., ventral and lateral dendrite; Stim. AD, antidromic stimulation; Stim. 8th, eighth nerve stimulation; Rec, recording electrode. Note that individual afferents may transmit electrotonically (e) and chemically (c) (9). Inhibitory interneurons (black) synapse on M cell dendrites as well as on the M cell soma. (*B* and *C*) Demonstration of the depression and its specificity in one experiment. (*B*) Superimposed averaged eighth nerve responses obtained 4 min before and 6 min after pairing the weak tetanization with antidromic stimulation. (*Insert*) Difference between the two waveforms, demonstrating that both the coupling potential and the excitatory postsynaptic potential (EPSP) decreased. (*C*) In contrast, EPSPs caused by stimulating the optic tectum increased slightly. (*D*) Time courses of changes in the coupling potential (○) and chemical EPSP (●) amplitudes in one depression experiment. For this and all other plots, 100% is the average response amplitude in the control period before tetanization, unless otherwise stated. Upward and downward arrows indicate onsets of protocols to produce potentiation and depression, respectively. For the first potentiation protocol, three strong stimuli at 500 Hz were repeated at 2-s intervals for 4 min, while for the second stronger one, five stimuli at 500 Hz and separated by 2-s intervals were applied for 6 min.

tended to gradually recover their control levels. The depression in the other two lasted throughout the recording period.

The depression in one of the latter two experiments was quite large, so that 40 min after the tetani, the amplitudes of both synaptic potentials were less than 20% of their control values. Its time course is illustrated in Fig. 1*D*. The two responses were depressed immediately after the pairing protocol, and they further decreased progressively over a period of 45 min. These depressions were reversible, as the responses recovered slightly after a weak potentiation protocol. A second depression paradigm again decreased them to their previous depressed levels, while a stronger potentiation protocol effectively reversed the LTD.

The efficacy of the synaptic connection between two neurons probably can vary only within a certain range, because the synaptic strength of a given connection is determined by the number of release sites, probability of release, and quantal size (14), and there are physical limits to the values of these parameters. Since synaptic strength could be raised and lowered by appropriate tetanizing paradigms, we questioned whether the efficacy of the synapses just before applying a tetanus influences the subsequent modulatory effect. To test this idea, four kinds of experiments were performed (Fig. 2): weak tetanizations alone or paired with antidromic stimuli were applied either in "naive" prepara-

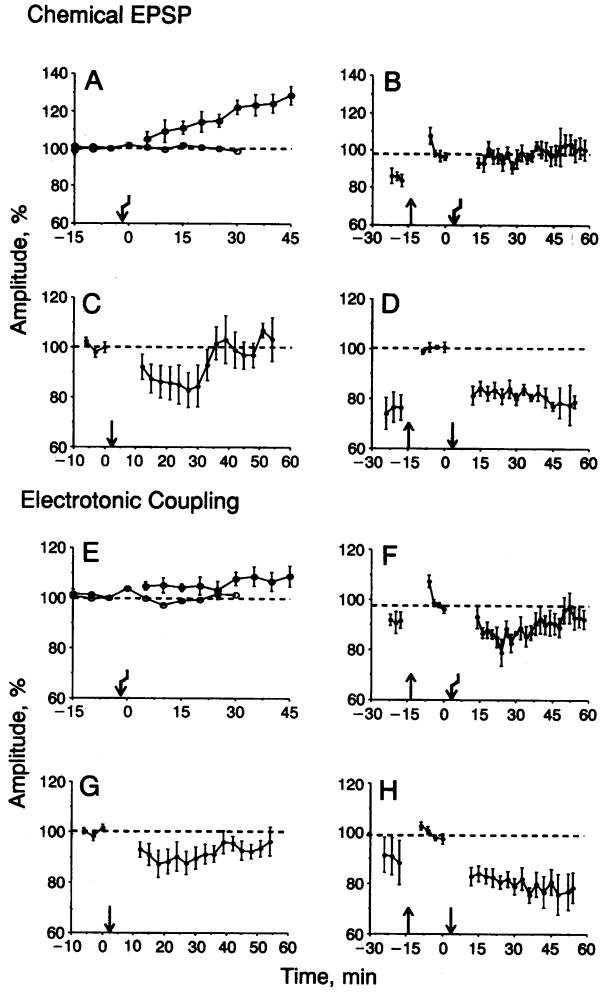

FIG. 2. Magnitude and duration of LTD depend upon the control level of synaptic efficacy. The plots compare long-term changes in the chemical EPSP (*A–D*) and the coupling potential (*E–H*) in four kinds of experiments: subthreshold tetanizations alone (jagged arrows) or paired with antidromic stimuli (downward arrows) were applied without prior tetanization or after synaptic strength had been raised by strong tetanizations (upward arrows). All data points are means ± SEM for five or more experiments, with the values of each expressed as percentage of the average response just before the last tetanizing protocol. Error bars are not shown for the controls (○, no tetanization). (*A* and *E*) Time courses of changes in chemical EPSP (*A*) and coupling potential (*E*) following weak tetanization alone. (*C* and *G*) Time courses of changes in chemical EPSP (*C*) and coupling potential (*G*) following weak tetanization paired with antidromic stimuli. (*B*, *D*, *F*, and *H*) Data from experiments in which synaptic efficacy was first raised by a potentiating protocol. Note that weak tetanization failed to produce any apparent enhancement in EPSP after a prior potentiation (*B*), but the coupling potential was clearly depressed (*F*). Also note that the depressions produced by the pairing protocol tended to last longer when preceded by potentiation (*D* and *H* vs. *C* and *G*).

tions or in those where synaptic strength was first raised by a stronger potentiating protocol. It should be noted that in those experiments where synaptic efficacy was raised first, the averaged synaptic response after the initial potentiation was used as the control. Thus, when a "depression" was induced afterwards, it was relative to the already elevated synaptic efficacy, although the responses might still have been higher than before the potentiation. We consider this is acceptable because activity-dependent changes in transmission from all levels of initial efficacy within the available operating range should be of equal importance.

In the absence of prior potentiation, weak tetanization alone ($n = 6$) produced a gradual potentiation of the chemical EPSP in five out of six experiments, ranging from 20% to 40% at 45 min after the training. In the remaining case there was a transient depression of about 15% for 10 min, followed by a slowly developing potentiation. The coupling potential in two of the cells was gradually potentiated by about 10% over a period of 40 min, while it changed minimally in another two and was slightly depressed by about 10% in the remaining two. When these results are pooled (Fig. 2), the averaged electrotonic coupling potential showed a slight increase (Fig. 2*E*; the grouped mean after the weak tetani was significantly higher than that of the control, $P < 0.01$), whereas the chemical EPSP was clearly potentiated, growing steadily to a peak enhancement of 25% on average over a period of 40 min (Fig. 2*A*).

However, when a moderate LTP was induced first, the same weak tetanization ($n = 5$) seemed to produce no further potentiation of the EPSP (Fig. 2*B*), and the coupling potential actually tended to decrease for about 20 min (Fig. 2*F*; use of the term "same tetanization" indicates that stimulus strengths were adjusted to produce equivalent postsynaptic responses). Analysis of the individual experiments revealed that the EPSPs were not altered by more than 5% in four of five experiments, and there was a lasting depression of about 20% in the fifth one. The coupling potentials in all five experiments were depressed for at least 10 min after the second tetani, with the magnitude of the effect ranging from 15% to 30%. This depression of the electrotonic coupling persisted throughout the recording period in two of five experiments and tended to recover gradually in the other three.

Thus, a tetanization that usually resulted in gradual potentiation of chemical transmission tended to produce no change when efficacy was first elevated, and the coupling potential was even depressed by such a protocol. That is, in the latter case, the sign of the modification was changed by moderately raising the synaptic efficacy. These differences were probably not due to simple occlusion, which might have occurred if synaptic efficacy and potentiation were already at their upper bounds. First, as the initial potentiations in Fig. 2 *B* and *F* were small, and we previously found that with stronger tetani LTP of "naive synapses" in this system averaged 60% for the EPSP and 25% for electrotonic coupling (13), there should have been reserves for further potentiations to occur. Indeed, in Fig. 2 *B* and *F*, the response amplitudes immediately following the strong tetanization are larger than their steady-state values, indicating that there was an additional upper range to synaptic strength; yet, the tetanizing protocols that usually produced potentiation (Fig. 2*A*, $P < 0.05$ at 15 min after the training) failed to do so (Fig. 2*B*, $P > 0.1$). Second, even if efficacy had been raised to its upper bound, this shift alone would not explain the depression of the electrotonic coupling in Fig. 2*F*.

As mentioned before, when each weak tetanus was paired with an antidromic stimulus without prior potentiation, there was a clear depression which lasted for at least 15 min in six of nine experiments. The averaged responses showed that the chemical EPSP tended to decrease for about 20 min, followed by a gradual recovery (Fig. 2*C*, $n = 8$; the pronounced effect illustrated in Fig. 1*D* was not included because its amplitude was more than two standard deviations away from the mean of the remaining experiments). The same sequence occurred with electrotonic coupling (Fig. 2*G*), although the late recovery was not as complete. When the same pairing protocol was applied after synaptic efficacy was first raised ($n = 6$), depressions of both the chemical EPSP (Fig. 2*D*) and the coupling potential (Fig. 2*H*) from their already elevated levels were produced in all six experiments. At 12 min after the training, the depression of the chemical EPSP ranged from 14% to 29% (mean = 21%), and that of the coupling potential ranged from 8% to 34% (mean = 22%). Furthermore, as shown in Fig. 2 *D* and *H*, the effect tended to last appreciably longer than did effects observed without prior potentiation (Fig. 2 *C* and *G*). Indeed, in these six experiments, depressions of the chemical EPSP and of the coupling potential lasted throughout the recording period in five and four cases, respectively.

In summary, the above data suggested that the depression was more likely to occur when the synaptic efficacy was raised with a prior strong tetanus, as it was found in 67% of naive preparations and 100% of those with an initial potentiation. Further, the depression tended to be relatively long lasting when synaptic efficacy was high, and transient when efficacy was low (Fig. 2 *C* vs. *D*, *G* vs. *H*). It should be pointed out, however, that the results in each plot of Fig. 2 describe the modification tendency observed by pooling data from a group of experiments, but the results from individual experiments were somewhat variable.

Although depression sometimes could be induced by tetanizing the eighth nerve alone (Fig. 2*F*), the data in Fig. 2 clearly illustrate the importance of the antidromic stimulus in generating this effect, regardless of whether the initial efficacy was low (Fig. 2 *A* vs. *C*, *E* vs. *G*) or high (Fig. 2 *B* vs. *D*, *F* vs. *H*). It is unlikely that the small depolarization of the M cell dendrite produced by the antidromic impulse (Fig. 3, *C*1, *C*2) plays an important role in depression, particularly since stronger tetanization, which fires the cell by activating more synapses, is the most effective means to induce potentiation (13). Given that antidromic stimulation also evokes a feedback inhibition that shunts the coupling potentials and the EPSPs during the tetanus (Fig. 3, *C*1 vs. *C*2), we suggest that the inhibition is more likely to underlie generation of LTD.

To test this idea, curare was used to block the synapses between the M cell and the relay neurons (15, 16), which excite the inhibitory interneurons. In the experiment of Fig. 3, potentiation (*B*1 vs. *B*2), depression (*B*3), and a second potentiation (*B*4) were induced sequentially while the brain was superfused with saline. (The control values at the beginning of this experiment decreased with time, but this drift does not affect the results, since the responses were stable after the first potentiation.) Addition of curare blocked the feedback inhibition, without altering the eighth nerve responses (Fig. 3 *C*2 vs. *C*3), and then the same pairing protocol failed to induce depression (Fig. 3 *A* and *B*4 vs. *B*5), indicating that pairing postsynaptic inhibition with weak presynaptic tetanization is the more appropriate condition for induction of LTD.

DISCUSSION

The above data suggest that LTD would appear to follow a Hebbian type rule, in that it occurs when postsynaptic inhibition effectively opposes weak presynaptic excitation. Since the activity of most neurons *in vivo* depends on the balance between excitatory and inhibitory inputs, this use-dependent depression of synaptic transmission could be one synaptic basis for many types of neural plasticity. Indeed, it

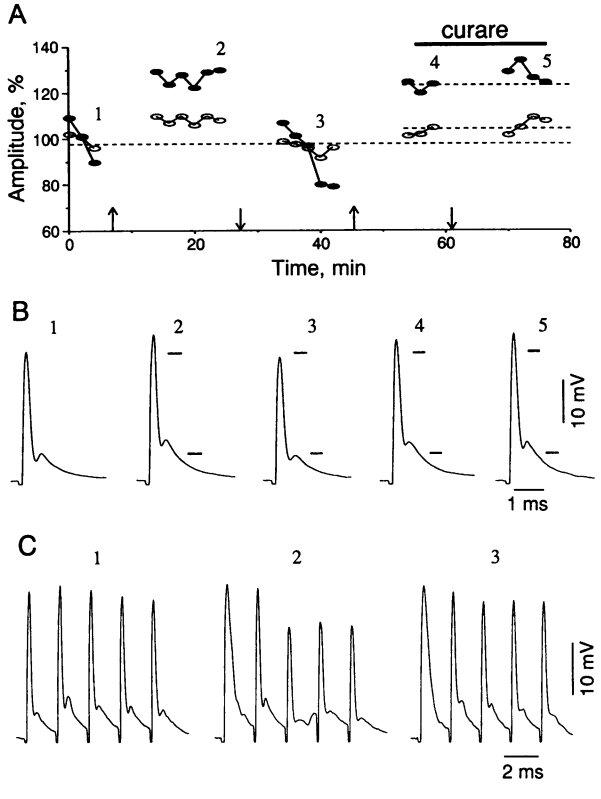

FIG. 3. Evidence for the role of inhibition in the depression induced by pairing antidromic stimuli with weak tetanizations. (*A*) Time courses of changes in the coupling potential (○) and chemical EPSP (●) amplitudes for one experiment. Upward and downward arrows indicate onsets of potentiation and depression paradigms, respectively. (*B*) Averaged eighth nerve responses obtained at the indicated times in *A*. Horizontal bars indicate control response amplitudes from the first trace. While the brain was superfused with saline, synaptic efficacy was first raised by a potentiation paradigm (1 vs. 2). A subsequent depression paradigm then reduced both the coupling and the chemical EPSP (2 vs. 3). Efficacy was raised again by a second potentiation paradigm (3 vs. 4), but after perfusion with curare [(+)-tubocurarine chloride, 3 mg in 40 ml of saline] blocked the feedback inhibition, depression could not be induced (4 vs. 5). (*C*) Evidence that curare blocks the feedback inhibition caused by an antidromic stimulus. 1, Postsynaptic responses to a subthreshold tetanus alone at 500 Hz. 2 and 3, Tetanus paired with an antidromic stimulus, the action potential being timed to occur synchronously with the first coupling potential. In the saline control (*C2*), the subsequent coupling potentials and EPSPs were shunted by feedback inhibition, while in the presence of curare (*C3*), this inhibitory shunt was abolished.

should be recognized that, in the M cell system, impulses of the eighth nerve also activate a disynaptic inhibitory pathway to the M cell, such that there is some inhibition associated with all tetanizations (12). The fact that a strong tetanus produces potentiation suggests that under those conditions excitation dominates. In fact, as the eighth nerve stimulus strength is increased, the inhibitory pathway saturates at a level where more excitatory afferents can still be recruited (12). In addition, feedback inhibition is activated both by powerful tetani that fire the M cell and by pairing the antidromic stimulus with weaker tetanizations (Fig. 1*A*), but in the first case, the excitation is greater and there is LTP (13), whereas the latter involves less excitatory input and causes depression. Thus, inhibition not only can block the occurrence of LTP as reported elsewhere (17) but also may contribute to an active depression of synaptic efficacy. It remains to be determined whether LTP and LTD have distinctly different thresholds or if the two processes can be triggered in parallel by certain stimulus paradigms. Regardless, these findings confirm the prediction (8) that the sign of a use-dependent modification of synaptic efficacy *in vivo* depends upon the balance of excitation and inhibition.

The mechanism by which postsynaptic inhibition contributes to the induction of depression is not clear. It could be due to the fact that inhibition shunts the excitatory responses, maintaining the membrane potential at a relatively hyperpolarized level. Alternatively, it may be a consequence of cross-talk between the inhibitory and excitatory postsynaptic receptors, possibly involving second-messenger systems.

As mentioned above, there are physical limits to the strength of a given synaptic connection. The results of this study show that the nature of the modulatory change in synaptic transmission produced by a certain tetanizing protocol depends upon the initial level of synaptic efficacy even when those limits are not reached. This finding is consistent with a theory of synaptic modification (18, 19), according to which a threshold (θ_M) determines the effect of a given level of instantaneous postsynaptic activity (c) (or dendritic depolarization), such that if $c > \theta_M$, potentiation will result, and if $c < \theta_M$, there will instead be depression. Moreover, θ_M is changeable and increases with the average level of recent postsynaptic activity ($\bar{c}$). This last point can explain some examples of developmental neural plasticity in visual cortex, such as the reversed suture experiment (19). Since $\bar{c}$ reflects the activity and strength of all synaptic inputs to a cell in a given period of time, θ_M for that cell has a single value and does not distinguish between different input pathways.

Our data do not rule out the possibility that θ_M of a given set of afferents increases as a function of their synaptic efficacy (Fig. 4; also compare Fig. 2 *A* vs. *B* and *E* vs. *F*). Thus, in contrast to the above theory, θ_M may not be the same for all inputs to a neuron but may have different values for different inputs. For example, suppose one of two input pathways to a cell is depressed and the other is potentiated. Then $\bar{c}$ of that cell may still be maintained at a high level due to activity in the latter pathway, and according to the original theory (18, 19), θ_M should be elevated for both inputs, requiring a higher level of dendritic depolarization for potentiation of either one. In contrast, we suggest that the θ_M of the weaker pathway should be low due to its low synaptic

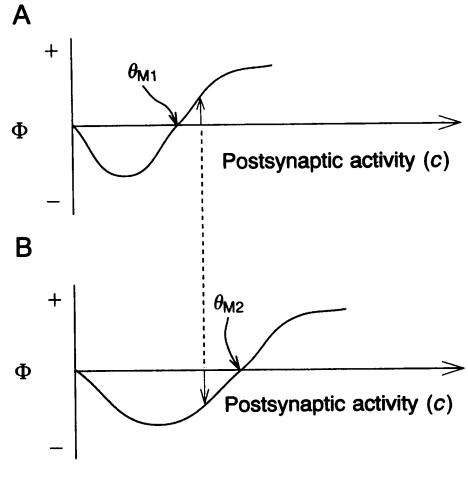

FIG. 4. The modification threshold, θ_M, increases with synaptic efficacy. Φ is a theoretical function defining how synaptic strength changes as a function of postsynaptic activity (c) or dendritic depolarization. (*A* and *B*) Plots of Φ vs. c for low (*A*) and high (*B*) levels of efficacy. θ_M is the threshold, or crossover point, for the shift from depression to potentiation, and is changeable (modified from ref. 19). When synaptic efficacy is increased, θ_M increases from θ_{M1} in the control (*A*) to θ_{M2} (*B*), so that the same level of postsynaptic depolarization (broken line) during a tetanization that usually produces potentiation (upward arrow in *A*) will fail to induce potentiation or even result in a depression (downward arrow in *B*).

efficacy, and it should require less postsynaptic depolarization to potentiate.

There is an alternative interpretation of the finding that prior tetanization influences the modifications evoked by subsequent training protocols: the effect could be due to some general changes in the M cell system produced by the strong initial tetanization itself, rather than to a change in synaptic efficacy of the tetanized pathway. However, the following observation suggests that the initial level of synaptic efficacy indeed plays an important role in activity-dependent modifications. In the M cell system, efficacy of chemical transmission varies from one afferent fiber to another, and in fact, many of the chemical synaptic connections are functionally silent (9). It is sometimes possible to selectively activate the weak or silent inputs with a low-strength test stimulus and to recruit relatively more strong ones when stimulus strength is increased. Then, the ratio of the coupling potential amplitude to that of the EPSP is greater for the weaker stimulus, with the coupling potential being proportional to the number of activated presynaptic fibers. When we compared the effects of a strong tetanization on these two responses in this special condition, most of the enhancement was due to potentiation of transmission at the initially weak connections. In other words, within a group of afferent fibers, potentiation was more likely to occur at the chemical synapses where the initial efficacy was low.

The above results further develop the recently proposed conditions for induction of homosynaptic LTP vs. LTD. While it has been suggested that the inductions of LTD and LTP depend on postsynaptic depolarization (8), it now appears that the thresholds for both are changeable. This might be one reason that LTP and LTD have not been observed consistently in many systems, for the synapses involved might not have been at the appropriate initial level of efficacy.

Finally, LTD had previously been described only for chemically mediated excitatory synapses, although electrotonic junctions are also found in higher structures such as hippocampus and neocortex (20). We have shown here that electrotonic coupling can also exhibit LTD, and that at mixed synapses in the goldfish brain, the two types of synaptic responses are often modified in parallel. This opens the possibility that activity-dependent changes of electrotonic synapses may also contribute to synaptic plasticity.

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