Glucocorticoid Receptor Activation Lowers the Threshold for NMDA-Receptor-Dependent Homosynaptic Long-Term Depression in the Hippocampus Through Activation of Voltage-Dependent Calcium Channels

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Cousens, Christine M., D. Steven Kerr, and Wickliffe C. Abraham. Glucocorticoid receptor activation lowers the threshold for NMDA-receptor-dependent homosynaptic long-term depression in the hippocampus through activation of voltage-dependent calcium channels. J. Neurophysiol. 78: 1–9, 1997. The effects of the glucocorticoid receptor agonist RU-28362 on homosynaptic long-term depression (LTD) were examined in hippocampal slices obtained from adrenal-intact adult male rats. Field excitatory post-synaptic potentials were evoked by stimulation of the Schaffer collateral/commissural pathway and recorded in stratum radiatum of area CA1. Low-frequency stimulation (LFS) was delivered at LTD threshold (2 bouts of 600 pulses, 1 Hz, at baseline stimulation intensity). LFS of the Schaffer collaterals did not produce significant homosynaptic LTD in control slices. However, identical conditioning in the presence of the glucocorticoid receptor agonist RU-28362 (10 μM) produced a robust LTD, which was blocked by the selective glucocorticoid antagonist RU-38486. The LTD induced by glucocorticoid receptor activation was dependent on N-methyl-D-aspartate (NMDA) receptor activity, because the specific NMDA receptor antagonist d(-)-2-amino-5-phosphonopentanoic acid (d-AP5) blocked the facilitation. However, the facilitation of LTD was not due to a potentiation of the isolated NMDA receptor potential by RU-28362. The facilitation of LTD by RU-28362 was also blocked by coinubcation of the L-type voltage-dependent calcium channel (VDCC) antagonist nimodipine. Selective activation of the L-type VDCCs by the agonist Bay K 8644 also facilitated LTD induction. Both nimodipine and d-AP5 were effective in blocking the facilitation of LTD by Bay K 8644. These results indicate that L-type VDCCs can contribute to NMDA-receptor-dependent LTD induction.

INTRODUCTION

Changes in synaptic efficacy have long been hypothesized to be important for memory formation in the CNS (Hebb 1949). Two forms of synaptic plasticity are long-term potentiation (LTP) and long-term depression (LTD). Although these forms of synaptic plasticity are primarily dependent on glutamatergic transmission for induction, it is apparent that they are subject to extrinsic modulation by classical neural transmitters and circulating hormones.

Stressful events release adrenal hormones [e.g., corticosterone (CORT)] that are known to interfere with acquisition of certain behavioral learning paradigms (Diamond and Rose 1994; Luine et al. 1994) and the induction of LTP (Foy et al. 1987; Shors et al. 1989). CORT has been shown previously to affect LTP induction in an “inverted U” dose-dependent fashion. Very low and high serum CORT titers (as might occur after adrenalectomy and stress, respectively) are associated with a suppression of LTP induction, whereas midrange titers are associated with robust LTP induction (Diamond et al. 1992; Kerr et al. 1994; Pavlides et al. 1993).

CORT activates two types of receptors, the mineralocorticoid receptor (type I) and the glucocorticoid receptor (type II). These receptors differ in both their affinity for CORT and their cellular effects. Mineralocorticoid receptors have a 10-fold higher affinity for CORT than glucocorticoid receptors (Joels and de Kloet 1990). At the trough of the circadian rhythm (i.e., low CORT levels), the mineralocorticoid receptors are tonically occupied, whereas at the peak of the circadian rhythm or under periods of stress, there is additional binding to the glucocorticoid receptors (de Kloet et al. 1987; Joels and de Kloet 1992). Activation of the mineralocorticoid receptor decreases the slow afterhyperpolarization (Joels and de Kloet 1990), thereby increasing the firing rate of a neuron to a maintained constant stimulus and thus enhancing neuronal excitability. Conversely, glucocorticoid receptor activation enhances the slow afterhyperpolarization (Joels and de Kloet 1989; Kerr et al. 1989), resulting in neuronal inhibition. The increase in the slow afterhyperpolarization is thought to be mediated by an increase of the calcium current through voltage-dependent calcium channels (VDCCs) (Karst et al. 1994; Kerr et al. 1992).

The opposing actions of the two corticosteroid receptors may account for the inverted U-shaped function relating CORT levels and LTP. Thus, under conditions in which mineralocorticoid receptors are selectively activated, CORT enhances LTP induction, whereas when glucocorticoid receptors are activated, LTP is suppressed (Kerr et al. 1994; Pavlides et al. 1993). CORT levels also alter the threshold for LTD induction; either exogenous CORT (Bennett et al. 1991) or selective activation of the glucocorticoid receptor (Kerr et al. 1994) increases the probability of inducing depression of the population spike following standard LTP induction protocols. This finding was confirmed in the dentate gyrus (Pavlides et al. 1995). Thus stimuli that are effective for inducing LTP under low-CORT conditions become effective for inducing LTD when the glucocorticoid receptor is activated. More recently, Kim et al. (1996) showed that
exposure to an uncontrollable stress in vivo facilitates subsequent N-methyl-D-aspartate (NMDA)-receptor-dependent LTD induction in vitro. Thus glucocorticoid activation widens the range of stimuli that are effective for LTD induction. Here we examine in more detail the mechanisms by which stress hormones facilitate LTD induction by using the selective glucocorticoid receptor agonist RU-28362. Our results indicate that glucocorticoid receptor activation effectively lowers the threshold for LTD induction, and that the enhancement of LTD is mediated partially by L-type VDCC activity. Aspects of this study have appeared in abstract form (Coussens et al. 1996; Kerr et al. 1996).

METHODS

Transverse hippocampal slices (400 μm) were prepared from young adult (200–250 g) adrenal-intact male Sprague-Dawley rats as previously reported (Kerr et al. 1994). In brief, animals were deeply anesthetized with gaseous methoxyflurane and rapidly decapitated. The hippocampus was dissected free in ice-cold medium and area CA3 was removed by a manual knife cut to eliminate possible development of seizure-like activity during stimulation. Slices were transferred to a submersion chamber and constantly superfused (1–2 ml/min) with an artificial cerebrospinal fluid (aCSF, saturated with 95% O₂-5% CO₂) consisting of (in mM) 124 NaCl, 3.2 KCl, 1.25 NaH₂PO₄, 26 NaHCO₃, 2.5 CaCl₂, 1.3 MgCl₂, and 10 d-glucose. Slices were allowed to equilibrate for 2 h before recording while the temperature was slowly raised to the recording temperature of 32.5°C.

A monopolar wire stimulating electrode (25–50 μm diam, stimulation current of 25–70 μA) was placed in the Schaffer collateral commissural pathway in area CA1. A glass recording electrode (1–3 MΩ) filled with 2 M NaCl was placed in stratum radiatum to record field excitatory postsynaptic potentials (EPSPs). Data were acquired and stored for off-line analysis with the use of an ASYST-based acquisition software developed in our laboratory. EPSP initial slopes (nV/ms) were measured and expressed as percent change from baseline values as previously reported (Kerr and Abraham 1995).

Slices exhibiting a maximal field EPSP amplitude <2.0 mV, signs of hyperexcitability, or unstable baseline potentials (drift of responses >10% over the 20-min baseline recording period) were discarded from the study. The stimulation intensity was adjusted to produce an 0.5-mV field EPSP amplitude during baseline stimulation (0.067 Hz). Conditioning stimulation consisted of two episodes of low-frequency stimulation (LFS, 1 Hz, 600 pulses at the baseline stimulation intensity) with 10 min between episodes. This “threshold” conditioning procedure has been shown to produce little or no LTD under control conditions (Kerr and Abraham 1995). Responses were monitored for 30 min post-LFS and LTD values are reported as mean percent change from baseline values ± SE recorded 25–30 min post-LFS.

In one series of experiments, NMDA-receptor-mediated potentials were isolated with the use of a solution containing 20 μM D-AP5 (PTX, 10 μM cyanotoxin-7-nitroquinolxaline-2,3-dione (CNQX), and 0.5 mM Mg²⁺. These potentials were monitored extracellularly, and were confirmed to be NMDA-receptor-dependent by bath application of 50 μM D(-)-2-amino-5-phosphono-pentanoic acid (D-AP5) at the end of the experiment.

RU-28362 and RU-38468 were gifts from Roussel UCLAF (Romainville, France). PTX and nimodipine were obtained from Sigma (St. Louis, MO), D-AP5, CNQX, and Sr(++) Bay K 8644 were obtained from Research Biochemicals International (Natick, MA). Except where noted, all drugs were in the aCSF for the duration of the recordings. RU-28362 and RU-38468 were added during the incubation period and remained in the superfusate for the duration of the experiment. The slices were exposed to the steroids for a minimum of 2.5 h before LFS. Nimodipine, Bay K 8644, RU-28362, and RU-38468 were dissolved in 95% ethanol and diluted to a final ethanol concentration of <0.1%. CNQX was dissolved in 0.1 mM NaOH and diluted to a final NaOH concentration of <0.01%. Experiments with nimodipine and Bay K 8644 were conducted in a darkened room.

Paired and Student’s t-tests were performed to assess group differences between the various treatments. Statistical significance was determined at a confidence level of P < 0.05.

RESULTS

LFS at 0.5-mV field EPSP strength in normal aCSF resulted in a short-term depression that returned to baseline by 30 min post-LFS (–3 ± 4%, mean ± SE, n = 6), in agreement with our previous findings (Kerr and Abraham 1995). However, the addition of the glucocorticoid receptor agonist RU-28362 (10 μM) =2 h before LFS led to the induction of a robust LTD (–27 ± 4%, n = 9, P < 0.01, Fig. 1A). The facilitatory effect of RU-28362 was not readily apparent until after the second bout of LFS. The facilitation of LTD was not due to a difference in incubation time between groups, and there was no apparent difference in the stimulus intensity required to evoke the 0.5-mV baseline test response. The facilitation was dose dependent, because conditioning in the presence of 1 μM RU-28362 failed to elicit an LTD significantly different from controls (–10 ± 3%, n = 4, Fig. 1B). Furthermore, coapplication of the specific glucocorticoid receptor antagonist RU-38468 (30 μM) (Mogulwsky and Philibert 1984; Philibert et al. 1991) prevented the facilitation of LTD by 10 μM RU-28362 (–4 ± 3%, n = 6, P > 0.1). Taken together, these data indicate that the RU-28362 effect is specific to the activation of glucocorticoid receptors.

In six slices, the competitive NMDA receptor antagonist D-AP5 (50 μM) was bath applied with the RU-28362 to test the NMDA receptor dependence of the RU-28362 effect. D-AP5 blocked the facilitation of LTD by RU-28362 (–9 ± 3%, n = 6, not significantly different from untreated controls, Fig. 2A). On washout of the D-AP5, LTD in the presence of RU-28362 induced a significant LTD (–23 ± 3%, n = 4, P < 0.01).

As noted, one action of glucocorticoid receptor activation is to increase the calcium current through VDCCs, including the L-type VDCC (Karst et al. 1994; Kerr et al. 1992). To assess whether the L-type calcium channel is involved in the RU-28362 facilitation of LTD, the specific L-type VDCC antagonist nimodipine (50 μM) was bath applied for the duration of the experiment. Threshold conditioning stimulation in the presence of both RU-28362 and nimodipine produced only a small response depression (–7 ± 5%, n = 6, Fig. 2B) that was not significantly different from baseline or from the values seen in control slices.

Because the RU-28362 facilitation of LTD is blocked by both nimodipine and AP5, it is possible that this is due to an upregulation of NMDA receptor function, leading to enhanced postsynaptic depolarization and thus enhanced VDCC activation. To examine this possibility, NMDA-receptor-mediated field EPSPs were isolated as described in METHODS. These potentials were monitored for 20 min; then 10 μM RU-28362 was added and the responses were re-
Selective activation of glucocorticoid receptors facilitates induction of homosynaptic long-term depression (LTD). A: 2 episodes of low-frequency stimulation (LFS, 600 pulses, 1 Hz at baseline stimulation strength, denoted by horizontal bars) induced only a short-term depression in control slices (−3 ± 4%, mean ± SE, ○, n = 6). In the presence of 10 μM RU-28362, however, LFS induced LTD (−27 ± 4%, ●, n = 9). Data in this and other figures are mean % change of baseline ± SE. Insets: sample traces (average of 5 sweeps) from baseline and 30 min post-LFS. Scale bar is 0.5 mV, 10 ms.

B: action of RU-28362 is dose dependent, because 10 μM but not 1 μM (−10 ± 3, n = 4) induced a significant LTD. Addition of 30 μM RU-38486 (specific glucocorticoid receptor antagonist) to the superfusate effectively blocked the facilitatory action of the agonist RU-28362 (−4 ± 3%, n = 6). Asterisk: significant difference from control group, P < 0.05.

recorded for a further 3 h. Instead of an increase in responses, RU-28362 administration led to a small decrease in the area under the curve of the NMDA-receptor-mediated potentials (−9 ± 7%, n = 5), which was not significantly different from the small decrease also observed for untreated controls (n = 4, Fig. 3). These data clearly indicate that the facilitation of LTD by RU-28362 is not due to an upregulation of NMDA receptor function. Later in the experiment, 50 μM nimodipine was added to the aCSF for the RU-28362-treated slices to see whether L-type VDCCs contribute to the evoked potential. Nimodipine application did lead to a further small decrease, supporting previous studies (Dingledine 1983; Novak et al. 1993). However, the control slices, which had not received nimodipine, also showed a small response decrement at the corresponding time in the experiment. Thus it remains unclear whether VDCCs contribute significantly to the NMDA-receptor-dependent evoked potentials under the present conditions. At the end of the experiment, d-AP5 (50 μM) was added to the perfusing medium and completely blocked the evoked potential, confirming that the field EPSP was mediated by NMDA receptors (Fig. 3).

To determine whether the facilitation of LTD by RU-28362 can be explained by a direct effect on L-type VDCCs, threshold conditioning stimulation was given in the presence of the selective L-type VDCC agonist Bay K 8644. Bay K 8644 (0.5 μM) caused a facilitation of LTD equivalent to that produced by RU-28362 (−26 ± 6%, n = 5, P < 0.02, Fig. 4A), and this effect was blocked by the coapplication of 20 μM nimodipine (−6 ± 3%, n = 4, P < 0.01 vs. Bay K 8644 alone, Fig. 4A). Similar to the RU-28362 facilitation, the LTD induced in the presence of Bay K 8644 was still dependent on the activation of NMDA receptors, because bath application of 50 μM d-AP5 prevented LTD induction in the presence of Bay K 8644 (−8 ± 5%, n = 5, P < 0.05 vs. Bay K 8644 alone, Fig. 4B).

The above findings indicate that L-type VDCCs can contribute to the induction of homosynaptic LTD. On the other hand, LTD has typically been reported to be primarily dependent on...
Facilitation of LTD by RU-28362 is dependent on N-methyl-D-aspartate (NMDA) receptor and L-type voltage-dependent calcium channel (VDCC) activation. A: addition of the NMDA receptor antagonist D-(-)-2-amino-5-phosphono-pentanoic acid (D-AP5, 50 μM) to the bathing medium markedly reduced induction of LTD in the presence of RU-28362, as measured 30 min post-LFS (−9 ± 3%, n = 6). On washout of D-AP5, responses were normalized to 0. LFS in the presence of only RU-28362 induced LTD (−23 ± 3%, n = 4). Insets: sample traces (average of 5 sweeps) from baseline (1), 30 min post-LFS (2), after washout of D-AP5 (3), and 30 min post-LFS (4). Scale bar: 0.5 mV, 10 ms. B: the L-type VDCC antagonist nimodipine (50 μM, present throughout experiment) completely blocked RU-28362 facilitation of LTD (−7 ± 5%, n = 6). Insets: sample traces (average of 5 sweeps) from baseline and 30 min post-LFS. Scale as in A.

**DISCUSSION**

The present experiments demonstrate that selective activation of glucocorticoid receptors facilitates homosynaptic LTD induction by threshold conditioning stimulation in a dose-dependent fashion. These results are consistent with the findings of Kim et al. (1996), who found that behavioral stress lowered the threshold for homosynaptic LTD induction as studied ex vivo. By applying the selective glucocorticoid receptor agonist RU-23862 directly to the slices, however, we have been able to exclude other physiological responses to stress, such as adrenal medullary hormone release, as necessary contributors to the LTD facilitation effect. These data suggest that the LTD facilitation observed by
Kim et al. (1996) may also have been due primarily to the activation of glucocorticoid receptors directly in the hippocampus. The possibility that activation of mineralocorticoid receptors is necessary, but not sufficient, to observe this effect cannot be ruled out, because in both studies tissue was obtained from adrenal-intact animals, which would be expected to exhibit occupation of these high-affinity receptors by circulating CORT. Additionally, it may be that dimers of activated mineralocorticoid and glucocorticoid receptors, which may increase the functional diversity of corticosteroid action (Trapp and Holsboer 1996; Trapp et al. 1994), mediate the facilitation of LTD.

**Facilitation of homosynaptic LTD and the role of VDCCs**

Although activation of L-type VDCCs has been reported to facilitate the induction of the heterosynaptic form of LTD in the hippocampus (Wickens and Abraham 1991), a block of VDCCs has not generally affected homosynaptic LTD (Kerr and Abraham 1995; Mulkey and Malenka 1992), with some exceptions (Bolshakov and Siegelbaum 1994; Christie et al. 1996; Otani and Conner 1996). In the present experiments, nimodipine blocked the LTD elicited in RU-28362, indicating that activation of L-type VDCCs is critical for this form of LTD. This finding is consistent with the fact that glucocorticoid receptor activation upregulates VDCCs in a protein-synthesis-dependent manner (Kerr et al. 1992). In addition, the similarity between the LTD facilitation by RU-28362 and that promoted by the L-type VDCC agonist BAY K 8644 in the present experiments supports the hypothesis that RU-28362 affects LTD through regulation of VDCCs. The BAY K 8644 experiments also confirm that L-type VDCCs contribute to homosynaptic LTD in adult rats under some circumstances.

Despite the reliance of RU-28362-facilitated LTD on VDCC activation, the LTD also remained NMDA receptor dependent, a finding consistent with the stress-induced facilitation of LTD observed by Kim et al. (1996). Thus it appears that L-type VDCCs can work cooperatively with NMDA receptors, and that at threshold levels of stimulation, activation of neither calcium channel alone is sufficient to generate LTD. The fact that at higher strengths of stimulation L-type VDCCs did not contribute to LTD suggests that their contribution at threshold is one of promoting NMDA receptor function, although we cannot rule out the possibility that under yet stronger activation conditions, VDCCs may
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FIG. 4. Selective upregulation of L-type VDCCs facilitates LTD induction. A: addition of the L-type VDCC agonist Bay K 8644 (0.5 μM) facilitated LTD induction as measured 30 min post-LFS (-26 ± 6%, ●, n = 5). This effect was blocked by coapplying the L-type VDCC antagonist nimodipine (20 μM, -6 ± 3%, ○, n = 4). Insets: sample traces (average of 5 sweeps) from baseline and post-LFS. Scale bar: 0.5 mV, 10 ms. B: Bay K 8644-facilitated LTD was still dependent on activation of NMDA receptors, because 50 μM D-AP5 prevented LTD (-8 ± 5%, n = 6). Insets: sample traces (average of 5 sweeps) from baseline and post-LFS. Scale bar shown in A.

mediate an NMDA-receptor-independent LTD (Otani and Connor 1996). Cooperative interactions could occur through a variety of means. For example, VDCC activation might 1) promote NMDA receptor activation by elevating membrane depolarization during synaptic activation, 2) add to the NMDA-receptor-mediated calcium transients occurring during synaptic stimulation, or 3) potentiate NMDA receptor function by activation of calcium-dependent protein kinases or phosphatases that regulate NMDA receptor function. In the present experiment we have shown that NMDA receptor function is not upregulated by RU-28362, thus ruling out the latter possibility. This finding is consistent with a previous report showing no change in NMDA receptor binding following stress (Clark and Cotman 1992). Although the voltage dependency of Ca$^{2+}$ influx through NMDA receptor channels was greatly reduced by lowering extracellular Mg$^{2+}$, the present experiment does not rule out the possibility of a contribution by VDCC activation to NMDA receptor channel function by a depolarization mechanism, when tested in normal medium.

A more indirect method for the promotion of LTD by VDCCs is also worth noting. Several labs have reported that activation of NMDA receptors during a period of hyperpolarization or synaptic inhibition successfully induces homosynaptic LTD (Debanne et al. 1994; Stanton and Sejnowski 1989; Thiels et al. 1994; Xie et al. 1992). In the present experiments, enhancement of VDCC activity by RU-28362 may promote calcium-dependent slow afterhyperpolarizations, thereby providing the postsynaptic hyperpolarization during synaptic stimulation that may be necessary to elicit
GLUCOCORTICOIDS FACILITATE LTD

Small increases in activity above resting levels will produce LTD, whereas greater activity will produce LTP. The crossover point between LTD and LTP is termed $\theta_M$. A similar model has been proposed by Artola and Singer (1993) (ABS rule), who use the term $\theta^+$ in the same way as the BCM model uses $\theta_M$, but additionally define the threshold for LTD as $\theta^-$. Because the plasticity thresholds are defined in terms of postsynaptic activity (BCM model), reflecting perhaps NMDA receptor activation (Bear et al. 1987) or the level of the postsynaptic calcium transient (ABS rule), then the activity level of a test pathway is only one determinant of which threshold, if either, is crossed. Activity in converging inputs, or modulatory influences by other neurotransmitter systems and circulating hormones, could also have a substantial impact. There is now considerable evidence that binding of corticosteroids to their receptors can influence the direction and degree of synaptic plasticity generated by a particular paradigm. The facilitation of LTD by RU-28362 was not evident until after the second bout of LFS. This pattern also occurs in control slices given conditioning stimulation above threshold for LTD induction (Kerr and Abraham 1995). It is thus apparent in both instances that although LTD is largely induced by the second bout of LFS, the first bout of LFS “primes” the synapses for the subsequent induction of LTD. This priming effect is similar to that previously reported for perforant path–granule cell synapses in vivo (Christie and Abraham 1992). The question is then raised as to whether RU-28362 acts by facilitating priming mechanisms or LTD induction / expression mechanisms. This is a difficult issue to resolve, and is one that also pertains to many other studies of LTD induced by long trains of LFS. For the present purposes, we have ascribed the RU-28362 action to the observable effect, namely, the facilitation of LTD, as is conventional for studies of this kind. However, once the mechanisms of LTD priming are better understood, it may become necessary to reassess whether stress hormones, and other modulatory neuroactive substances, have a primary mode of action on priming rather than specific LTD mechanisms.

Regulation of synaptic plasticity thresholds by stress hormones

The Bienenstock, Cooper, and Munro (BCM) (Bienenstock et al. 1982) model of synaptic plasticity suggests that there is a function (\(\Phi\)) describing the relation between postsynaptic activity (as driven by afferent activity) and synaptic modifications (Fig. 6A). Small increases in activity above resting levels will produce LTD, whereas greater activity will produce LTP. The crossover point between LTD and LTP is termed $\theta_M$. A similar model has been proposed by Artola and Singer (1993) (ABS rule), who use the term $\theta^+$ in the same way as the BCM model uses $\theta_M$, but additionally define the threshold for LTD as $\theta^-$. Because the plasticity thresholds are defined in terms of postsynaptic activity (BCM model), reflecting perhaps NMDA receptor activation (Bear et al. 1987) or the level of the postsynaptic calcium transient (ABS rule), then the activity level of a test pathway is only one determinant of which threshold, if either, is crossed. Activity in converging inputs, or modulatory influences by other neurotransmitter systems and circulating hormones, could also have a substantial impact. There is now considerable evidence that binding of corticosteroids to their receptors can influence the direction and degree of synaptic plasticity generated by a particular paradigm. The
induction of LTP (Diamond et al. 1992; Kerr et al. 1994; Pavlides et al. 1993), as well as homosynaptic LTD (Kerr et al. 1994), varies as an inverted U-shaped function of plasma CORT titers. The lack of LTP when there are high titers appears to be due to glucocorticoid receptor activation, because this effect is mimicked by RU-28362 administration. Thus tetanization that normally gives a weak LTP will produce LTD in the presence of RU-28362 (Pavlides et al. 1995). These data, combined with the findings that stress and RU-28362 lower the threshold for homosynaptic LTD induction, suggest that glucocorticoid receptor activation may spread the function in both directions, effectively shifting $\theta^+$ to the left and $\theta_m$ ($\theta^+$) to the right (Fig. 6A). The net effect of these shifts is to increase the probability of LTD induction across a wider set of stimulation parameters, and to make LTP harder to elicit. It should be noted that these threshold shifts refer to the level of afferent activity that normally is required to induce LTD or LTP, and not necessarily to subsequent biophysical or biochemical events (e.g., the level of postsynaptic calcium critical for triggering LTD or LTP) that are induced by such activity.

Although the model in Fig. 6A appears to account reasonably well for the stress and RU-28362 data, there is at least one other interpretation. Recent evidence from both the dentate gyrus and area CA1 of the hippocampus suggests that if afferent activity is taken to an extreme, then the function curls toward zero again, and less LTP is obtained (Abraham and Huggett 1997; Barr et al. 1995; Christie et al. 1995). With the use of this model, the RU-28362 effects on synaptic plasticity might be explained by an overall shift to the left of the function (Fig. 6B). Establishing which of these two models is a better representation of the RU-28362 effects on plasticity will require a detailed examination across a wide range of stimulation parameters.

Summary and conclusions

The present experiments demonstrate that activation of glucocorticoid receptors effectively lowers the threshold for homosynaptic LTD induction in the hippocampus of mature rats, a finding in good correspondence with a recent demonstration that stress exerts the same effects (Kim et al. 1996). Thus, although homosynaptic LTD is more difficult to induce in mature rats relative to juveniles (Dudek and Bear 1992), it is clear that the threshold for this form of LTD is dramatically reduced under specific, naturally occurring physiological conditions such as stress or hippocampal theta rhythm (Huerta and Lisman 1995; Pavlides et al. 1988). Thus homosynaptic LTD is readily brought into play at times when memory storage is likely to be of utmost importance.

Our experiments indicate that RU-23862 facilitates LTD induction in a novel way, by promoting L-type VDCC activation. It is interesting, however, that this LTD nonetheless remains NMDA receptor dependent. These results suggest that L-type VDCCs may work synergistically with NMDA receptors to induce LTD under normal physiological conditions, and therefore contribute to the facilitation of LTD during stress or aging, which are characterized by an elevation of circulating CORT (Kim et al. 1996; Norris et al. 1996). The contribution by L-type VDCCs to LTD becomes redundant, however, under stronger induction conditions that sufficiently activate NMDA receptors.

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