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Differential Effect of TEA on Long-Term Synaptic Modification in Hippocampal CA1 and Dentate Gyrus *in vitro*

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The effectiveness of tetraethylammonium (TEA) and high-frequency stimulation (HFS) in inducing long-term synaptic modification is compared in CA1 and dentate gyrus (DG) *in vitro*. High-frequency stimulation induces long-term potentiation (LTP) at synapses of both perforant path-DG granule cell and Schaffer collateral-CA1 pyramidal cell pathways. By contrast, TEA (25 mM) induces long-term depression in DG while inducing LTP in CA1. The mechanisms underlying the differential effect of TEA in CA1 and DG were investigated. It was observed that T-type voltage-dependent calcium channel (VDCC) blocker, Ni^{2+} (50 μM), partially blocked TEA-induced LTP in CA1. A complete blockade of the TEA-induced LTP occurred when Ni^{2+} was applied together with the NMDA receptor antagonist, D-APV. The L-type VDCC blocker, nifidipine (20 μM), had no effect on CA1 TEA-induced LTP. In DG of the same slice, TEA actually induced long-term depression (LTD) instead of LTP, an effect that was blocked by D-APV. Neither T-type nor L-type VDCC blockade could prevent this LTD. When the calcium concentration in the perfusion medium was increased, TEA induced a weak LTP in DG that was blocked by Ni^{2+}. During exposure to TEA, the magnitude of field EPSPs was increased in both CA1 and DG, but the increase was substantially greater in CA1. Tetraethylammonium application also was associated with a large, late EPSP component in CA1 that persisted even after severing the connections between CA3 and CA1. All of the TEA effects in CA1, however, were dramatically reduced by Ni^{2+}. The results of this study indicate that TEA indirectly acts via both T-type VDCCs and NMDA receptors in CA1 and, as a consequence, induces LTP. By contrast, TEA indirectly acts via only NMDA receptors in DG and results in LTD. The results raise the possibility of a major synaptic difference in the density and/or distribution of T-type VDCCs and NMDA receptors in CA1 and DG of the rat hippocampus.

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INTRODUCTION

Various intracellular concentrations of calcium, $[Ca^{2+}]_i$, play a determinant role in inducing either long-term potentiation (LTP) (Jahr & Stevens, 1987; Lynch, Larson, Kelso, Barrionuevo, & Schottler, 1983; Malenka, 1991; Mayer & Westbrook, 1987) or long-term depression (LTD) (Christofi, Novicky, & Bindman, 1991; Dudek & Bear, 1993; Hirsch & Crepel, 1992) of glutamatergic synapses. Namely, large increases in $[Ca^{2+}]_i$ lead to the induction of LTP, whereas small increases in $[Ca^{2+}]_i$ result in LTD (Lisman, 1989). The increased intracellular calcium needed for the induction of LTP or LTD can be introduced via multiple calcium-conducting channels. The induction of NMDA receptor-dependent LTP/LTD requires calcium influx into the postsynaptic region via the activated NMDA receptor/channel. High-frequency stimulation (HFS) can induce LTP in both CA1 and dentate gyrus (DG) regions through activation of NMDA receptors (Bliss & Collingridge, 1993). It is also possible to induce an LTP that is NMDA receptor *in*dependent by deriving calcium from other sources. One of the sources is voltage-dependent calcium channels (VDCCs) (Grover & Teyler, 1990; Miyakawa et al., 1992). Bath application of the K^+ channel blocker, tetraethylammonium (TEA), for 7 to 10 min could induce a novel type of LTP (TEA LTP) in CA1 region (Aniksztejn & Ben-Ari, 1991). The induction of TEA LTP was first shown to be NMDA receptor independent because the NMDA receptor antagonist, D-APV, failed to block the induction of TEA LTP (Aniksztejn & Ben-Ari, 1991). Although others later reported that TEA LTP also partially depended on the activation of the NMDA receptors (Huber, Mauk, & Kelly, 1995), all studies have agreed that the critical induction event for TEA LTP was calcium influx via ionic channels other than NMDA receptors/channels, for example, L-type VDCC (Aniksztejn & Ben-Ari, 1991; Huang & Malenka, 1993). In contrast to the multiple studies of CA1, the effect of TEA in the DG region has not been investigated intensively. The only report available suggests that TEA also induced LTP in DG and that the TEA LTP was T-type VDCC dependent (Coogan, O'Leary, & O'Connor, 1999). Until now, no studies have been conducted to compare TEA effect on these two regions in the same *in vitro* slice.

In this study, we first conducted a series of experiments in which field excitatory postsynaptic potentials (EPSPs) were recorded simultaneously from DG and CA1 of a single slice. Differential effects of TEA both on the induction of LTP and on the profile of EPSPs in the two regions were found and investigated. Our results demonstrate that the induction of TEA LTP in CA1 occurs via both NMDA-dependent and NMDA-independent mechanisms. The T-type VDCC is the main mediator for the NMDA-independent component in CA1. For the DG, by contrast, TEA could induce neither NMDA-dependent nor NMDA-independent LTP but instead induced an NMDA-dependent LTD (TEA LTD).

METHODS

Hippocampal slices were prepared from adult male Sprague–Dawley rats (200–250 g). Animals first were anesthetized with 5% halothane, then were decapitated, and the

hippocampi then were rapidly dissected. Both hippocampi were sectioned into blocks while being washed with cold oxygenated medium, and slices of tissue (400 microns thick) then were cut perpendicular to the longitudinal axis using a vibratome. Slices were incubated with medium consisting of 128 mM NaCl, 5 mM KCl, 1.25 mM $NaH2PO_4$, 26 mM $NaHCO_3$, 10 mM glucose, 2 mM $CaCl_2$, and 2 mM $MgSO_4$, aerated with 95% O_2/5% CO_2. Hippocampal slices were maintained at 32°C throughout the entire experiments. During the recording session, slices were transferred to the recording chamber and perfused at flow rates of 4 to 6 ml/min; the perfusion medium was changed to include 1 mM $MgSO_4$ and 100 μM picrotoxin (Sigma). Bipolar nichrome stimulating electrodes were placed in the medial perforant path and Schaffer collateral to orthodromically activate dentate granule cells and CA1 pyramidal cells, respectively. A cut was made between the CA3 and CA1 regions to prevent epileptiform activity in the CA3 region from affecting the recording in CA1. During the application of TEA (25 mM, Sigma), the concentration of NaCl was changed correspondingly to maintain constant osmolarity of the perfusion medium. D-APV (50 μM, Tocris), nickel chloride (50 μM, Aldrich), or nifidipine (20 μM, Sigma) was added to the perfusion medium when used. Nifidipine was made daily as a 10-mM stock in dimethyl sulfoxide (DMSO), stored in dark, and diluted to 20 μM final concentration in the perfusion medium immediately prior to application. Application of the DMSO (0.05%) alone had no effect on the LTP and EPSPs. Field EPSPs of the DG granule cell and/or CA1 pyramidal cell were evoked at a frequency of 0.1 Hz by 0.1 ms duration impulses (intensity: 0.04–0.12 mA) and were recorded with microelectrodes. The extracellular field EPSPs of CA1 were recorded in stratum radiatum, and the extracellular field EPSPs of DG were recorded in the middle third of the molecular layer. The extracellular recording pipettes were filled with 2 M NaCl (resistance: 1–2 MΩ). The intracellular recording pipettes were filled with 3 M potassium acetate (impedance: 100 MΩ). High-frequency stimulation consisted of four stimulation trains separated by 5-s intervals. Each train had 10 impulses at a frequency of 100 Hz and was delivered at the same intensity as that used to evoke baseline responses. All evoked responses were amplified, digitized, and stored using a PC. Data from different slices were combined by normalizing amplitudes of EPSPs relative to the average response amplitudes measured during the control period. Student's *t* test was used for statistical comparisons.

RESULTS

TEA Induces Robust LTP in CA1 but Weak LTD in DG

The effectiveness of TEA and high-frequency stimulation in inducing synaptic modification was compared for CA1 and dentate gyrus by recording simultaneously from both sites of a single slice. High-frequency stimulation induced robust LTP in both CA1 and DG (Figs. 1A and 1B). Tetraethylammonium (25 mM) also induced robust LTP in CA1 that lasted at least 60 min (Fig. 1C). The amplitude of TEA LTP in CA1, measured 50 to 60 min following 10 min of TEA application, was 74 ± 13% of baseline ($p < .001$, $n = 9$). This TEA LTP did not significantly occlude the HFS LTP (data not shown). In contrast to the effects of TEA in CA1, a weak but significant LTD was induced in DG 30 to 60 min following TEA application (Fig. 1D). The amplitude of this LTD was −12 ± 3% of baseline 50 to 60 min after TEA application ($p < .01$, $n = 14$).

Another marked differential effect of TEA, which might be the cause for the above differential effect on the synaptic modification, was observed on the EPSP profile during TEA application. In CA1, a large late component in field EPSPs that lasted $>$ 100 ms was observed with a 15-ms latency (Fig. 1E(b)). In DG, a short, rapidly decayed late component in field EPSPs was observed with a 15-ms latency (Fig. 1F(b)).

Intracellular recording showed that there was no significant change in resting membrane potentials before, during, or after TEA application. Bursts of action potentials were observed in CA1 pyramidal cells (Fig. 1G) but not in DG granule cells (Fig. 1H). Consistent with the field EPSP results, TEA induced potentiation of the intracellular EPSPs in CA1 ($n = 3$), but depression in DG measured 60 min after termination of TEA application ($n = 4$).

L-Type VDCC Blocker Nifidipine Does Not Block the TEA LTP/LTD in CA1/DG

The role of L-type VDCCs in the induction of TEA LTP/LTD was investigated by including nifidipine (20 μM) in the perfusion medium. Results showed that nifidipine did not block the TEA LTP in CA1 or TEA LTD in DG. The amplitude of TEA LTP in CA1, measured at 50 to 60 min after TEA application, was 61 $\pm$ 9% of baseline ($p >$ .10, $n = 5$) (Fig. 2A). In the same slice, the amplitude of TEA LTD in DG, measured 50 to 60 min after TEA application, was -9 ± 4% of baseline ($p > .10$, $n = 4$) (Fig. 2B).

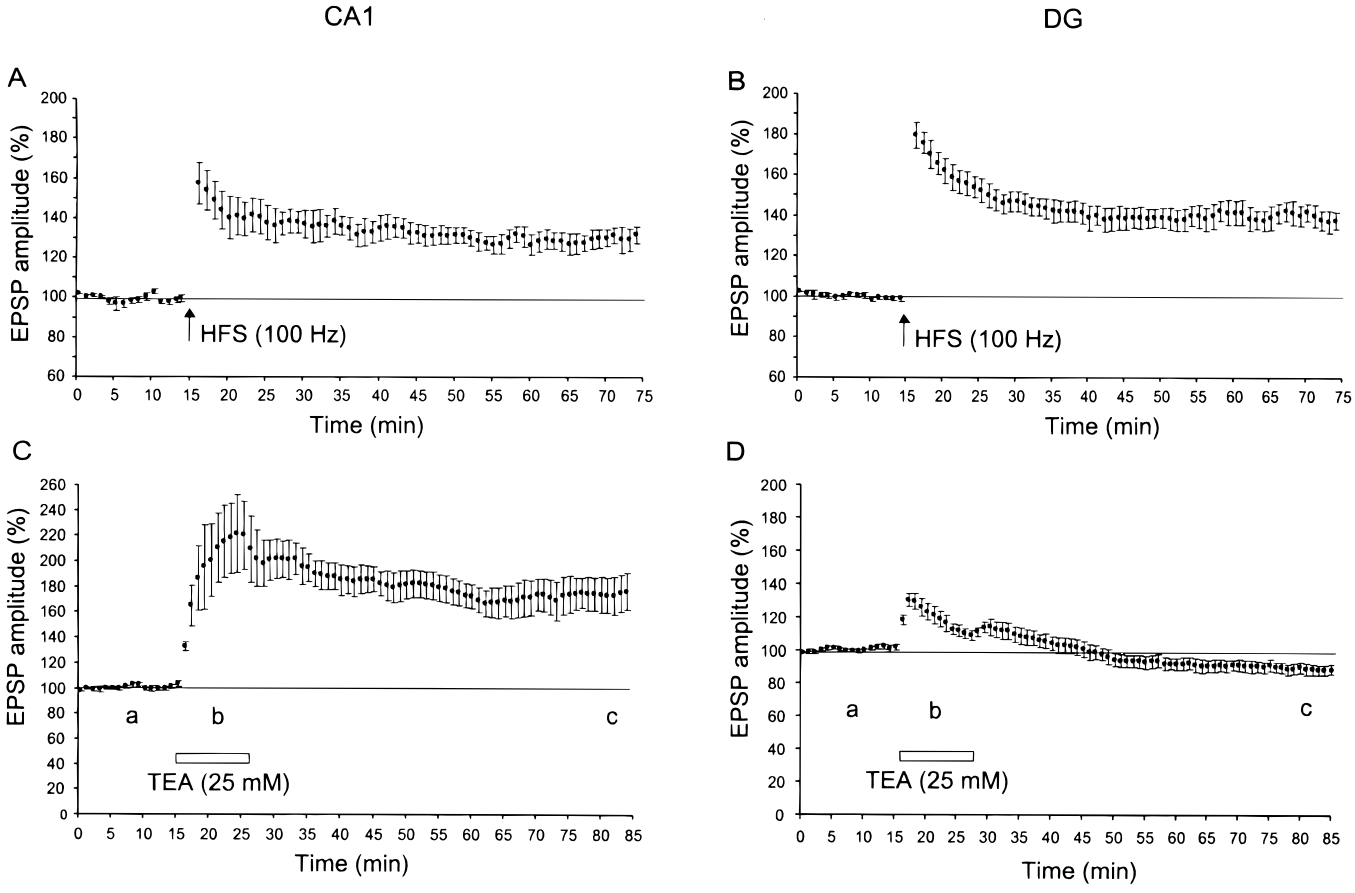
D-APV Partially Blocks the TEA LTP in CA1 and Completely Blocks the TEA LTD in DG

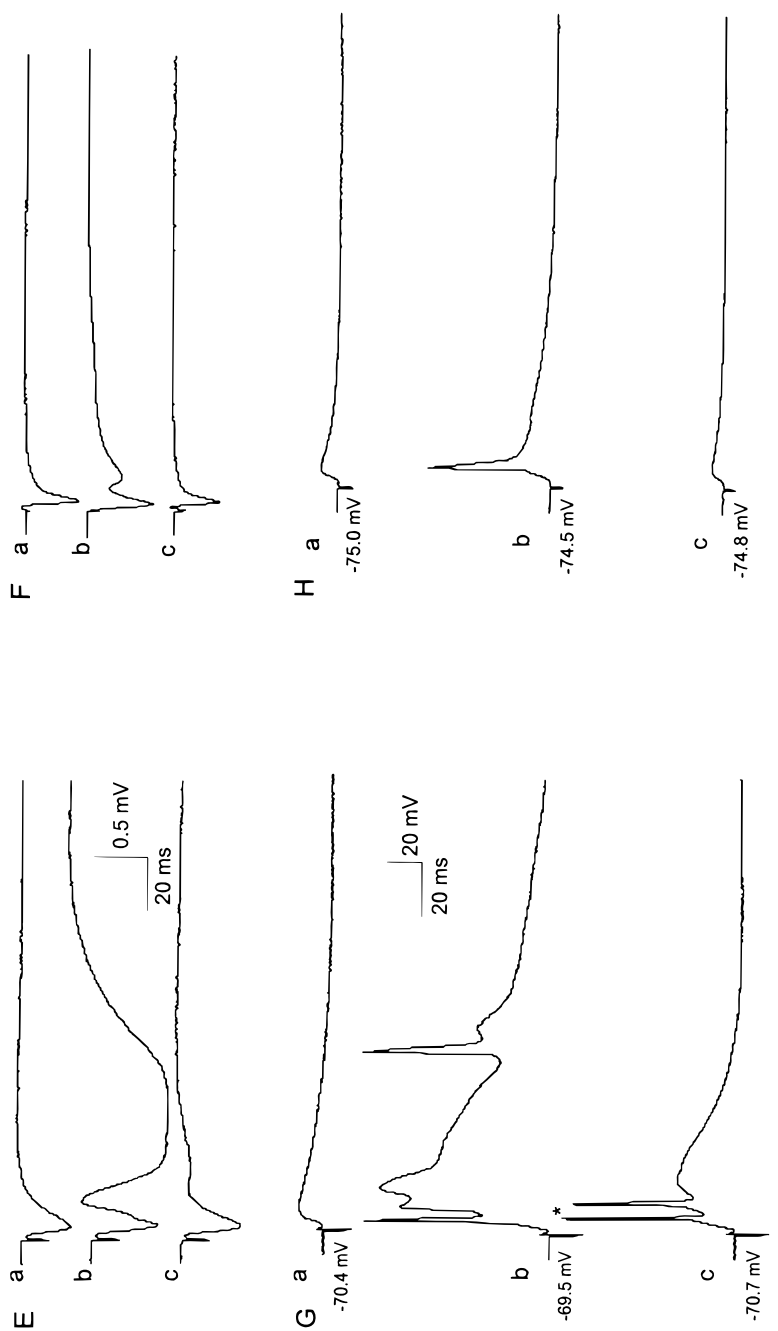
To determine the contribution of NMDA receptors to the induction of TEA LTP/LTD, D-APV (50 μM) was applied to the bath. Recordings showed that D-APV did not alter the baseline amplitude of EPSPs in either CA1 or DG. However, D-APV partially blocked the induction of TEA LTP (29 $\pm$ 6%, $p < .001$, $n = 5$) (Fig. 2C). In the same slice, the TEA LTD in DG was blocked completely (1 $\pm$ 6%, $p < .05$, $n = 5$) (Fig. 2D).

Ni^{2+} Partially Blocks the TEA LTP in CA1, and a Combination of Ni^{2+} and D-APV Strongly Blocks the TEA LTP in CA1

The role of T-type VDCCs in the induction of TEA LTP in CA1 was investigated. Ni^{2+} (50 μM), a T-type VDCC blocker, did not alter the amplitude of the baseline EPSPs. But

FIG. 1. Comparison of HFS- and TEA-induced synaptic modification in CA1 and DG. (A) HFS (100 Hz) induced LTP in CA1. (B) HFS (100 Hz) induced LTP in DG. (C) TEA (25 mM) induced LTP in CA1. (D) TEA (25 mM) failed to induce LTP in DG. A 10-min bath application of 25 mM TEA resulted in a weak but significant LTD in DG. In all of the following graphs: (a) before TEA application; (b) during TEA application; (c) 60 min after wash-out of TEA. (E) Representative field EPSPs recorded from stratum radiatum in CA1. Note that TEA resulted in a large late component in addition to enhancing the fast component of EPSPs. (F) Representative field EPSPs recorded from the middle third of the molecular layer in DG. (G) Representative intracellular EPSPs recorded from a pyramidal cell in CA1. Note that membrane potentials were barely changed during TEA application in both pyramidal and granule cells. Bursts of action potentials were present in the CA1 pyramidal cell (*) but not in the DG granule cell. (H) Representative intracellular EPSPs recorded from a granule cell in DG.


CA1
DG
A
B
C
D
EPSP amplitude (%)
HFS (100 Hz)
Time (min)
a
b
c
TEA (25 mM)


E
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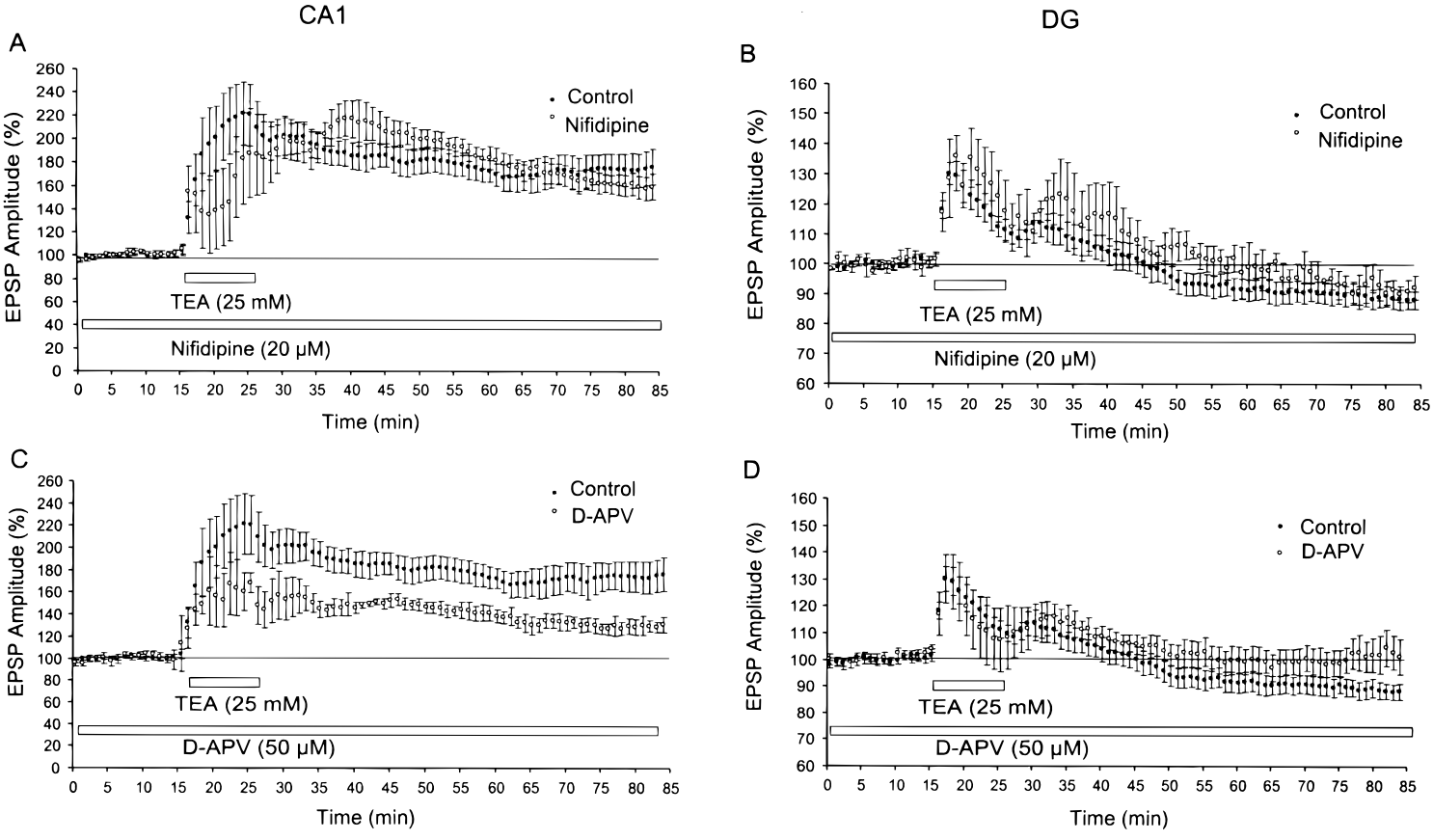
CA1
DG
A
B
C
D
EPSP Amplitude (%)
Time (min)
Control
Nifidipine
TEA (25 mM)
Nifidipine (20 μM)
D-APV
D-APV (50 μM)

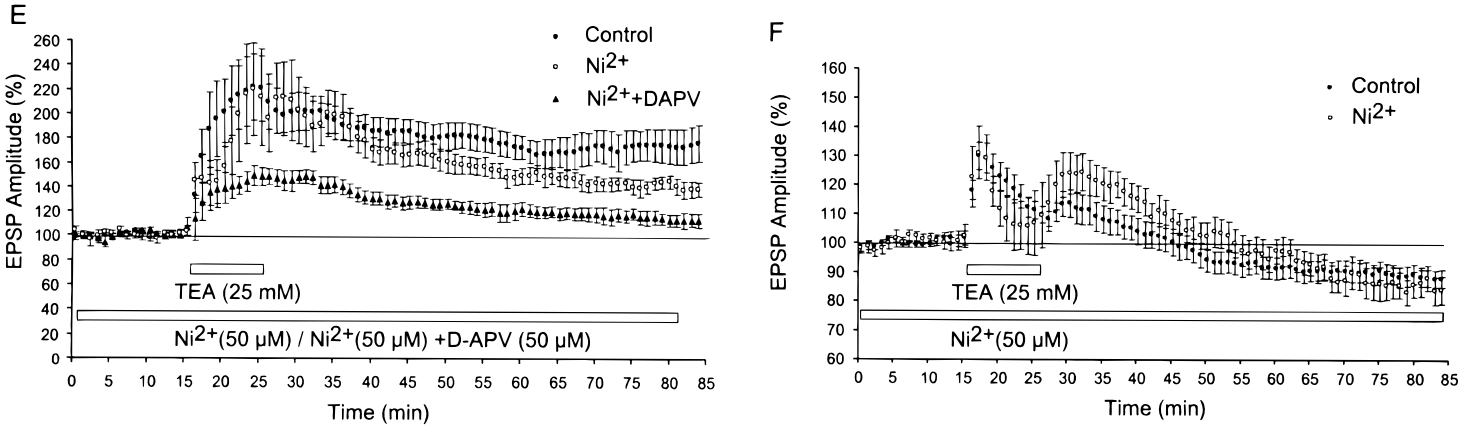

FIG. 2. The induction of TEA LTP in CA1 is both NMDA receptor and T-type VDCC dependent, whereas TEA LTD in DG is only NMDA dependent. (A) L-type VDCC blocker, nifidipine (20 μM) did not block the TEA LTP in CA1 (open circles). In all graphs, closed circles represent the TEA LTP/LTD under control condition. (B) Nifidipine (20 μM) did not block the TEA LTD in DG (open circles). (C) D-APV (50 μM) partially blocked the TEA LTP in CA1 (open circles). (D) D-APV (50 μM) blocked the TEA LTD in DG (open circles). (E) Ni^{2+} (50 μM) partially blocked the TEA LTP in CA1 (open circles). A combined application of Ni^{2+} (50 μM) and D-APV (50 μM) strongly blocked the TEA LTP in CA1 (closed triangles). (F) Ni^{2+} (50 μM) did not block the TEA LTD in DG (open circles).

the TEA LTP in CA1 was reduced to 41 ± 6% in the presence of Ni^{2+} ($p < .01$, $n = 5$) (Fig. 2E). When a cocktail of D-APV (50 μM) and Ni^{2+} (50 μM) was applied to the bath, the TEA LTP in CA1 was strongly inhibited (14 ± 5%, $p < .001$, $n = 6$) (Fig. 2E).

Ni^{2+} significantly decreased the late component of the EPSPs (Fig. 3B(a)). The combination of Ni^{2+} and D-APV more strongly decreased the late component of EPSPs to a very low level that approached that observed under control conditions (Fig. 3B(a)).

Ni^{2+} Does Not Block the TEA-Induced LTD in DG

As shown above, Ni^{2+} (50 μM) partially blocked the TEA LTP in CA1. In the same slice, the TEA LTD in DG was not blocked by Ni^{2+} (Fig. 2F). The amplitude of LTD, measured 50 to 60 min after TEA application, was −14 ± 5% of the baseline ($p > .10$, $n = 6$). Baseline recordings showed that Ni^{2+} at the concentration used in our experiments did not alter the amplitude of EPSPs in DG.

High Extracellular Ca^{2+} Concentration Reverses TEA LTD in DG in a T-Type VDCC-Dependent Manner

TEA elicited a late component of both field EPSPs and intracellular EPSPs from DG neurons that was much smaller in magnitude compared to that observed for CA1. Ni^{2+} could significantly eliminate the late component in CA1 (Fig. 3B(a)), indicating that it is mediated primarily by an inward calcium current. As a result, calcium impacts in a much smaller magnitude are expected in the activated postsynaptic region of DG granule cells than in that of CA1 pyramidal cells. Because LTD has been linked to small increases in calcium, and LTP has been linked to large increases in calcium, it is possible that TEA may result in LTP in DG instead of LTD if the late component caused by TEA is increased. To test this hypothesis, we increased the concentration of Ca^{2+} in the perfusion medium from 2 to 4 mM. The higher concentration of Ca^{2+} markedly increased the late component of EPSPs in DG (Fig. 3B(b)). Interestingly, a weak LTP was also observed (Fig. 3A). The amplitudes of EPSPs, measured 20 to 30 min and 50 to 60 min after TEA application, were 13 ± 4% ($p < .05$) and 4 ± 6% ($p > .05$) of the baseline, respectively ($n = 5$). Ni^{2+} (50 μM) blocked the late component (Fig. 3B(b)) as well as the weak LTP induced in 4 mM Ca^{2+} in DG (Fig. 3A). Tetraethylammonium LTD was unmasked after the blockade (−16 ± 8%, $p < .05$, $n = 4$). Changing TEA concentration (ranging from 12.5 to 50 mM) had no significantly different effect on the TEA LTD in DG (data not shown).

DISCUSSION

The major finding of this series of studies is that TEA application differentially affects synaptic transmission and long-term synaptic plasticity in the CA1 and DG fields of the *in vitro* hippocampus. Specifically, TEA induces robust LTP in CA1 but LTD in DG. The induction of LTP in CA1 is both T-type VDCC and NMDA receptor -dependent, whereas the induction of LTD in DG is exclusively NMDA receptor dependent.

NMDA-independent LTP was first revealed by Grover and Teyler (1990) using HFS (200 Hz) and then by Aniksztejn and Ben-Ari (1991) applying TEA. Several earlier reports following these initial findings showed that L-type VDCC activation alone was required

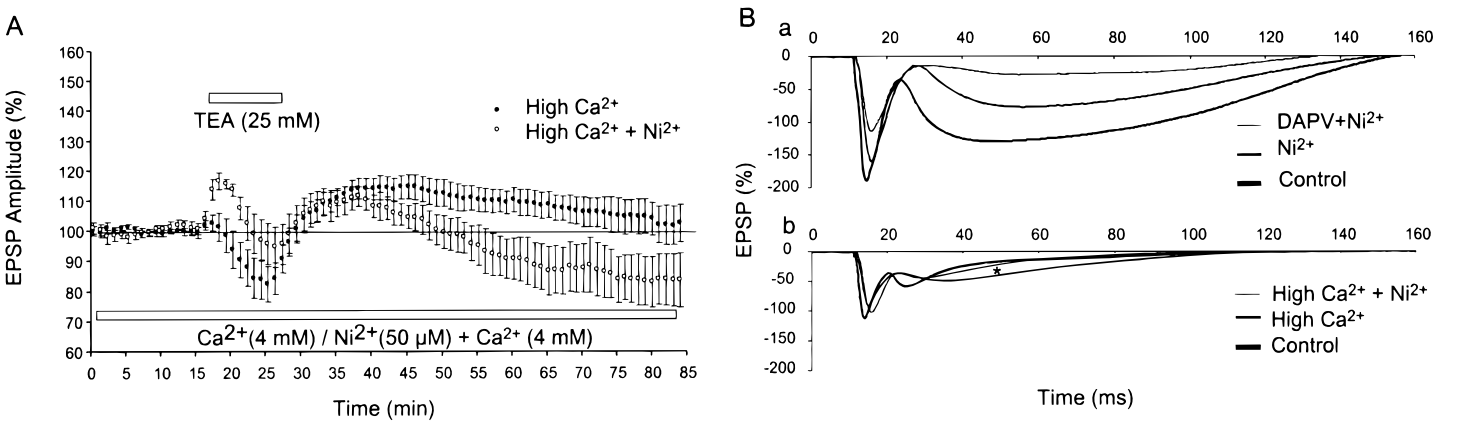

FIG. 3. The TEA-elicited late component in DG is increased by raising extracellular Ca^{2+} concentration, resulting in the reversal of TEA LTD. The late component in both CA1 and DG is mediated chiefly by T-type VDCC. (A) In medium with doubled Ca^{2+} concentration (4 mM), TEA induced weak LTP in DG (closed circles). This LTP was reversed by Ni^{2+} (50 μM) application (open circles). (B(a)) EPSP waveforms during the TEA application in CA1. In both panels B(a) and B(b), EPSPs were first averaged and normalized within single slices and then averaged across different slices ($n = 9$). Note that the large late component was partially blocked by Ni^{2+} (50 μM) application (medium line) and strongly blocked by the combined application (thin line) of Ni^{2+} (50 μM) and D-APV (50 μM), compared to the late component under control condition (thick line). (B(b)) EPSP waveforms during the TEA application in DG ($n = 14$). Note that in 4 mM Ca^{2+} medium (medium line), the late component increased significantly (*) compared to the late component in 2 mM Ca^{2+} medium (thick line). This increase was blocked by Ni^{2+} (50 μM) application (thin line).

for the induction of this type of LTP in CA1 (Huang & Malenka, 1993). Subsequently, it was shown that TEA could induce LTP via both VDCC- and NMDA receptor-mediated mechanisms (Huber et al., 1995). However, there is still controversy concerning the identity of the VDCC channel type involved. Consistent with an earlier report (Hanse & Gustafsson, 1994), we found that the VDCC component was not blocked by the L-type VDCC blocker nifidipine. We report here that it instead is blocked by Ni^{2+}, indicating that T-type VDCCs are more likely to be involved in the induction process. The involvement of the T-type VDCC rather than other types of VDCCs in the induction of TEA LTP receives further support from the comparison between the properties of the T-type VDCC and those of other types of VDCCs. For example, the voltage range in which the T-type VDCC is activated (i.e., from -50 to $+70$ mV peaked at 0 mV) is substantially lower than that of the other types of VDCCs such as the L-type, which has an activation range between -20 and $+70$ mV peaked at $+30$ mV (Bean, 1985). In fact, because of the voltage activation property of the T-type VDCC, sub-threshold EPSPs in dendrites are able to open the T-type VDCC and induce a local increase in intracellular calcium (Magee et al., 1995). Tetraethylammonium has been recently shown to be able to induce LTP in DG (Coogan et al., 1999). In their study, however, Coogan et al. (1999) used younger rats, $\sim$70–150 g, which would correspond to $\sim$25 to 40 days old, whereas we conducted our experiments using rats more than 2 months old. Therefore, age may be a factor in determining whether TEA induces LTP or LTD in DG such as down-regulation of T-type VDCC during this restricted developmental period. We did observe that a weak LTP could be induced by TEA application when the concentration of calcium in the perfusion medium was raised to 4 mM.

Several mechanisms, either singularly or in combination, may be responsible for the differential cell region-specific effect of TEA in eliciting the enhanced late EPSP component and in inducing LTP/LTD. The first involves factors that govern the magnitude of calcium currents. It is known that the resting membrane potential of DG granule cells *in vitro* is more hyperpolarized than that of CA1 pyramidal cells (Schwartzkroin, 1975; Staley, Otis, & Mody, 1992). Consequently, the same level of depolarization applied to DG and CA1 cell fields will result in lower levels of VDCC and NMDA receptor/channel activation in DG compared to CA1. Thus, TEA application would be expected to result in lower levels of calcium influx in DG relative to CA1. Long-term depression induced in DG has been demonstrated (Thiels, Xie, Yeckel, Barrionuevo, & Berger, 1996; Xie, Berger, & Barrionuevo, 1992) to be associated with lower levels of depolarization compared to those that induce LTP. Based on these previous findings, we expected that TEA would induce LTP in DG if it was able to introduce greater calcium influx. To test this possibility, we raised calcium concentration in the perfusion medium and found that TEA could indeed induce LTP in DG in the presence of higher levels of extracellular calcium. However, the magnitude of that late EPSP component and LTP was still small in absolute terms and much smaller than that observed in CA1. In addition, this TEA-induced LTP could be prevented by the VDCC blocker Ni^{2+} alone, in contrast to TEA-induced LTP in CA1 that could be prevented by either NMDA receptor antagonism or VDCC channel blockade (Huber et al., 1995). On the other hand, it has been widely documented that HFS can reliably induce LTP in both DG and CA1 pathways. Taken together, it seems that the difference in resting membrane potential between the cell types alone cannot easily explain the differential effects of TEA in these two subregions of hippocampus.

The second set of mechanisms that could account for the differential effect of TEA in CA1 and DG involves factors that control the effective intracellular calcium concentration. It has been reported that calbindin-D_{28k}, a calcium binding protein, is much more abundant in dentate granule cells than in CA1 pyramidal cells (Sloviter, 1989). Thus, even if calcium influx into the two different cell types were equivalent, the effective intracellular calcium concentration might be sufficiently lower in granule cells, compared to CA1 pyramidal cells, to account for the induction of LTD rather than LTP in DG. Although this set of mechanisms might account for the differential effect on synaptic plasticity, it cannot explain the differential effect of TEA on the calcium influx, that is, the difference in the magnitudes of the late EPSP components in CA1 and DG.

The third set of mechanisms to be considered involves potential differences in the density and/or distribution of NMDA and VDCC channels in CA1 pyramidal and dentate granule cell membranes. During TEA application, a large late EPSP component appeared in CA1 that could be substantially blocked by Ni^{2+}. The late EPSP component in CA1 cannot possibly result from intensified recurrent activities in CA3 given that we have severed the connections between CA3 and CA1 during slice preparation. It also cannot result from increased fast EPSP component alone given that increasing the magnitude of EPSPs by raising stimulus intensity could not elicit the late component (data not shown). Therefore, the large late component is specifically due to the effect of TEA. Assuming that the density of T-type VDCC is higher in the postsynaptic membrane of the CA1 pyramidal cell than in that of the DG granule cell, the differential effect of TEA on the late EPSP component can be explained as follows. In the presence of TEA, the inward calcium current via T-type VDCC is so large for the CA1 pyramidal cell that it becomes self-sustaining by counteracting the repolarization process, whereas the inward calcium current in the DG granule cell is not large enough to counteract the repolarization process and, hence, quickly wanes. This may account for why the late component was much smaller in magnitude in DG. Because the repolariztion process relies on outward potassium currents, it is possible that the late EPSP component might reflect different potassium channel properties between these two cell types. Our results, however, do not support this possibility, given that changing TEA concentration (ranging from 12.5 to 50 mM) had no significantly different effect on the late component, whereas increasing extracellular calcium concentration could enlarge the magnitude of the late EPSP component in DG, resulting in a weak LTP. In summary, our results and the above analyses favor the third set of mechanisms (i.e., different density/distribution of VDCC and possibly NMDA) as the main factor that underlies the differential effects of TEA found in this study.

The differential effects of TEA found in this study strongly suggest that the plastic capacity of the perforant path–granule cell pathway is inherently weaker—in terms of the dynamic range, number of induction mechanisms, and so on—than that of the Schaffer collateral–pyramidal cell pathway. The proposed difference in distribution/density of VDCC and NMDA, if confirmed by further studies, and its differential consequence revealed by TEA application in our studies may have important implications in understanding the functional significance of each node of the trisynaptic loop in hippocampus.

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