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Synaptic disinhibition during maintenance of long-term potentiation in the CA1 hippocampal subfield

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ABSTRACT **Long-term potentiation (LTP) in the CA1 region of the hippocampus is widely believed to occur through a strengthening of efficacy of excitatory synapses between afferent fibers and pyramidal cells. An alternative mechanism of LTP, reduction of efficacy of synaptic inhibition, was examined in the present report. The present study demonstrates that the maintenance of LTP in the CA1 hippocampal subfield of guinea pigs is accompanied by impairment of type A γ-aminobutyric acid (GABA) receptor function, particularly at apical dendritic sites of CA1 pyramidal cells. Enhanced excitability of GABAergic interneurons during LTP represents a strengthening of inhibitory efficacy. The net effect of opposite modifications of synaptic inhibition during LTP of CA1 pyramidal cells is an overall impairment of the strength of GABAergic inhibition, and disinhibition could contribute importantly to CA1 pyramidal cell LTP.**

Excitatory glutamatergic synapses are the proposed sites of the persistently enhanced excitatory responses during long-term potentiation (LTP) in the CA1 hippocampal subfield: potentiation of synaptic responses may occur presynaptically by increased release of the excitatory transmitter glutamate (1–3) or postsynaptically by an enhancement of the sensitivity of α-amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid (AMPA) receptors or a combination of pre- and postsynaptic mechanisms (4, 5).

In spite of the attention excitatory transmission processes have received in connection with LTP, potentiation of excitatory responses after tetanization could theoretically occur through impairment of synaptic inhibition. Type A γ-aminobutyric acid ($GABA_A$) receptor-mediated synaptic inhibition plays a critical role in the control of excitation in the mammalian central nervous system (6). Several studies have reported short-term changes of synaptic inhibition in connection with high-frequency stimulation (7–9). During the maintenance phase of LTP, however, orthodromically evoked early inhibitory postsynaptic potentials (IPSPs) are generally not reduced (10–12). Furthermore, postsynaptic GABA sensitivity was found to be unchanged during LTP in an extracellular study (13), and in several studies the excitability of GABAergic interneurons was found to be unchanged or even increased during LTP (14–16). These results have led to a general belief that disinhibition does not contribute to pyramidal-cell hyperexcitability during the maintenance phase of LTP. Stronger or repetitive tetanization paradigms revealed that IPSPs (17–20) and GABA sensitivity (19) were in fact decreased after tetanization. In the present study, possible changes of the strength of $GABA_A$ receptor-mediated inhibition during maintenance of LTP were examined in the CA1 hippocampal subfield. Intracellular recordings were carried out in pyramidal cell somata and apical dendrites and in interneurons in strata lacunosum/moleculare (L/M), pyramidale, and alveus/oriens (A/O).

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MATERIALS AND METHODS

Brain Slices. Transverse hippocampal slices (21, 22) of 450 μm thickness (cut on a McIlwain tissue chopper) from adult guinea pigs (Hartley; 150–200 g) were superfused in an interface recording chamber (Fine Science Tools, Belmont, CA) by a solution saturated with 95% O_2/5% CO_2 (temperature, 30–32°C) of the following composition: 118 mM NaCl, 3 mM KCl, 25 mM $NaHCO_3$, 1.2 mM NaH_2PO_4, 1.2 mM $MgCl_2$, 1.7 mM $CaCl_2$, and 11 mM D-glucose.

Intracellular Recordings. The standard content of the glass pipettes (WPI Instruments, Waltham, MA) used as recording electrodes was KOAc (4 M, 40- to 80-MΩ electrode resistances) or Li_2SO_4 [1 M, in combination with Lucifer yellow (LY), see below, 70–159 MΩ]. Cl^--containing electrodes [3 M KCl, 35–80 MΩ; 1 M LiCl (+LY), 50–130 MΩ] were used to monitor spontaneous IPSPs (sIPSPs) (23) (see Fig. 2).

Stimulation. Evoked responses were elicited by stimulation of stratum radiatum Schaffer collateral/commissural fibers through a pair of insulated tungsten bipolar electrodes (stimulation range, 15–400 μA). Tetanic stimulation (50 or 100 Hz; 1 s; single-pulse duration, 80 μs) was applied via the same stimulation electrode.

Drugs. Bicuculline, picrotoxin (PTX), 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX), 2-amino-5-phosphonopentanoic acid (AP5), and saclofen were applied by bath perfusion. CNQX, D-AP5, and saclofen were purchased from Tocris Neuramin (Bristol, U.K.); all other drugs were from Sigma.

Iontophoresis. Iontophoretic $GABA_A$ responses were elicited by application of $GABA_A$-receptor agonists muscimol (50 mM, pH 3.5, in extracellular solution) or GABA (1 M, pH 3.5, in the presence of bath-applied $GABA_B$-receptor antagonist saclofen, 100 μM) in CA1 pyramidal cells through a double- or triple-barreled extracellular iontophoretic electrode with one channel containing extracellular solution for current balancing (ejecting currents, +5 to +140 nA; retaining currents, −3 to −20 nA). The iontophoretic electrode was positioned by an independent micromanipulator as close as possible to the respective recording site.

Data Acquisition. Data (voltage responses from the recording electrode) were digitized and stored on disk (Nicolet 410 oscilloscope) for subsequent off-line analysis.

LY Staining and Histology. LY staining (26–28) was performed in 17 (of 57) apical dendritic recordings (29, 30) and 26 (of 55) interneuron recordings (31) for morphological confirmation of cell type. The tip of the electrode was back-filled with LY (1.5% in 1 M Li_2SO_4 or LiCl) whereas the shaft was filled with 1 M Li_2SO_4 or LiCl alone. Dye injection was implemented by repetitive 400-ms hyperpolarizing current pulses (between −0.5 and −1 nA DC; 5–10 min; 0.5 Hz)

Abbreviations: AP5, 2-amino-5-phosphonopentanoic acid; A/O, alveus/oriens; CNQX, 6-cyano-7-nitroquinoxaline-2,3-dione; EPSP, excitatory postsynaptic potential; GABA, γ-aminobutyric acid; HP, holding potential; IPSP, inhibitory postsynaptic potential; sIPSP, spontaneous IPSP; L/M, lacunosum/moleculare; LTP, long-term potentiation; PT, posttetanus (after tetanus); PTX, picrotoxin; V_{rest}, resting potential; LY, Lucifer yellow.

during the recording procedure. The histological method used represents a slightly modified procedure as previously described (28). Stained cells were viewed by epifluoresence microscopy (Nikon Optiphot-2) and photographed.

RESULTS

LTP: Orthodromic IPSPs in CA1 Pyramidal Cell Somata and Dendrites. Intracellular recordings in CA1 pyramidal cells, somata in stratum pyramidale, or apical dendrites in stratum radiatum revealed a typical sequence of postsynaptic potentials upon conditioning stimulation of the Schaffer collateral fiber pathway (orthodromic stimulation): a fast excitatory postsynaptic potential (EPSP) followed by an early and a late IPSP (see Fig. 3). Application of a standard tetanus produced LTP [enhancement of the orthodromic EPSP >30 min posttetanus (PT 30)] in 96 of 117 CA1 pyramidal cell somata (Table 1). Potentiation of 10% or more of the orthodromic EPSP amplitude 30 min PT was used as the defining criterion for "maintenance" of LTP.

In accordance with data from previous studies (10–12), changes of the early ($GABA_A$-mediated) IPSP amplitudes during LTP were variable: in those 96 CA1 pyramidal cell somata that exhibited long-term EPSP increases, early IPSPs were enhanced in 37 cells (as depicted in Fig. 1*B*), unchanged in 39 cells, and decreased in 20 cells (Table 1).

Tetanization-induced modifications of synaptic transmission are thought to occur at dendritic synapses near activated fibers. Recordings from CA1 pyramidal cell dendrites were performed in stratum radiatum (29, 30) (Fig. 1). Tetanization produced a long-term enhancement of the orthodromic EPSP in 45 of 57 dendrites, no change of the EPSP in 8 dendrites, and a reduction of the EPSP in 4 dendritic recordings (Table 1). In contrast to somatic recordings in which the early IPSP was decreased in only 20 of 96 LTP exhibiting recordings, amplitudes of early IPSPs were reduced in 34 of 45 dendritic recordings during LTP, unchanged in 8 (of 45), and increased in 3 (of 45) recordings (Fig. 1, see Fig. 3, and Table 1).

Table 1. Effects of tetanization on postsynaptic potentials and $GABA_A$ responses in CA1 neurons

Recording cells	% total cells examined		
	Increased	Unchanged	Decreased
Interneurons: EPSP			
Basket (26)	65.4 (17)	11.5 (3)	23.1 (6)
L/M (15)	80.0 (12)	6.7 (1)	13.3 (2)
A/O (14)	78.6 (11)	14.3 (2)	7.1 (1)
Pyramidal cells: EPSP			
S (117)	82.1 (96)	10.2 (12)	7.7 (9)
D (57)	79.0 (45)	14.0 (8)	7.0 (4)
Pyramidal cells: Early IPSP			
S (96)	38.5 (37)	40.6 (39)	20.8 (20)
D (45)	6.7 (3)	17.8 (8)	75.5 (34)
Pyramidal cells: Iontophoretic $GABA_A$ conductance			
S (27)	3.7 (1)	25.9 (7)	70.4 (19)
D (21)	0 (0)	9.5 (2)	90.5 (19)

Tetanization-induced changes of the orthodromic EPSP peak amplitude in interneurons and pyramidal cell somata (S) and dendrites (D) measured 30 min PT. Interneurons represent homogeneous groups with respect to tetanization-induced changes of EPSP amplitudes ($\alpha > 0.1$, χ^2; df = 4). Interneurons were identified by site of recording in the CA1 subfield and morphological (LY staining) and physiological (see ref. 31) criteria. S and D were not significantly different with respect to EPSP amplitudes ($\alpha > 0.1$, χ^2; df = 2). Early IPSP (see Fig. 1) and iontophoretic $GABA_A$ conductance (see Fig. 3) were measured in CA1 pyramidal cells that exhibited LTP. S and D were significantly different with respect to IPSP changes ($\alpha < 0.001$, χ^2; df = 2) but not with respect to iontophoretic $GABA_A$ conductance changes ($\alpha > 0.1$, χ^2; df = 2). Classification of recordings as decreased or increased denote respective changes of >10% over pretetanus controls. Numbers in parentheses are absolute numbers of cells examined (n).

In 10 pairs of synchronous intracellular recordings in somata and dendrites in which both the dendritic and the somatic recordings exhibited LTP (Fig. 1), 7 of 10 dendrites but only

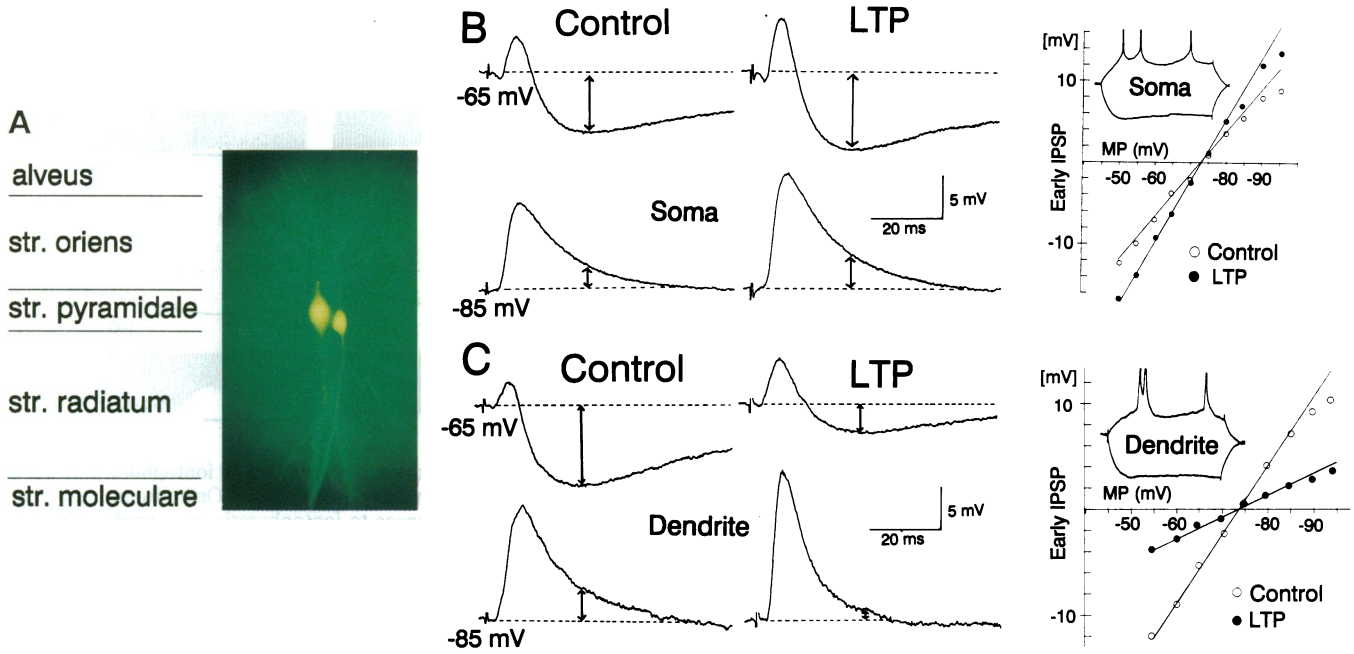

FIG. 1. LTP: $GABA_A$-mediated orthodromic IPSPs in the soma and dendrite of CA1 pyramidal cells. Synchronous intracellular recordings in CA1-pyramidal-cell soma (in stratum pyramidale) and apical dendrite (in stratum radiatum, 250 μm from stratum pyramidale). (*A*) LY injection revealed a pyramid-like shape and location in stratum pyramidale of somata of both recordings and a bipolar arrangement of dendritic processes in both cells. A burst-like response to depolarizing current was observed in the dendritic recording, and single action potentials and the absence of bursts were observed in the somatic recording (*B* and *C Insets* at the right). (*B* and *C*) (*Left*) Orthodromic responses before (Control) and 30 min PT (LTP) recorded at −65 and −85 mV (marked by arrows). (*Right*) Graphs of peak of the early IPSP in the same cells before and 30 min PT at various HPs.

2 of 10 somata exhibited a reduction of early IPSPs during LTP. In addition, an enhancement of the early IPSP during LTP was seen in 4 of 10 somata and in none of the dendrites.

The graph of early IPSP amplitudes recorded at various holding potentials (HPs) in apical dendrites (Fig. 1*C*) during LTP shows IPSP reduction at all HPs. The reduction was somewhat larger at depolarized HPs, probably due to tetanization-induced impairment of outward rectification (Fig. 1*C*). The changes of IPSP amplitudes during LTP (variable changes in somata and decreases in dendrites, Table 1) were not accompanied by a shift of the reversal potential of $GABA_A$-mediated IPSPs (Fig. 1 *B* and *C*): in dendrites, the early IPSP reversed at -77.5 ± 1.8 mV before and -78.1 ± 1.3 mV 30 min PT (mean ± SEM; $n = 8$; $P > 0.1$, paired t test); in somata, the early IPSP reversed at -78.43 ± 1.5 mV before and -76.95 ± 2.3 mV 30 min PT ($n = 12$, $P > 0.1$).

LTP: sIPSPs. sIPSPs generated by spontaneous discharges of interneurons are depolarizing when recorded with chloride-filled electrodes at resting potential (V_{rest}), persist during blockade of excitatory transmission (CNQX at 20 μM and D-AP5 at 10 μM), and are reversibly blocked by the $GABA_A$-receptor antagonist bicuculline (50 μM) (data not shown) (see ref. 23). sIPSP amplitudes were reduced during LTP in both somata and dendrites (in the cell depicted in Fig. 2 from 1109 control events per min to 729 during LTP). The amplitude–frequency histogram of sIPSPs in Fig. 2*B* demonstrates that during LTP the number of high-amplitude sIPSPs was reduced to a far greater extent than low-amplitude sIPSPs: <5% of control sIPSPs with peak amplitudes 3 mV and higher were counted during LTP as compared to ≈80% of control sIPSPs with 1- to 2-mV amplitudes and 102% of control sIPSPs with 0.2- to 1-mV amplitudes. The tetanization-induced shift of the amplitude–frequency profile of sIPSPs (similar to the one depicted in Fig. 2) was statistically significant (by use of χ^2 test, $\alpha < 0.05$) in 10 of 12 somatic and 9 of 10 dendritic pyramidal-cell recordings.

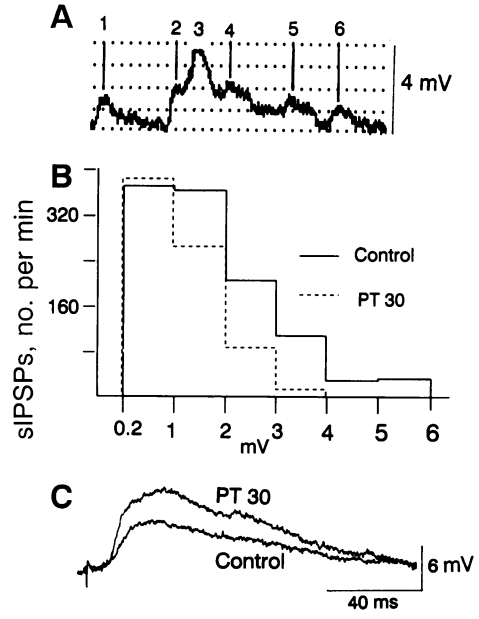

FIG. 2. LTP: sIPSPs in CA1-pyramidal-cell soma. (*A*) sIPSPs were measured as depolarizing events >0.2 mV [monophasic PSPs (peaks 1 and 6) or discernible peaks riding on a complex wave (peaks 2–5)]. (*B*) Amplitude–frequency histogram of spontaneous depolarizing events before and 30 min PT (PT 30) in an individual cell. Distribution of sIPSPs was significantly different 30 min PT ($\chi^2 = 144.55$, $\alpha < 0.001$, df = 11). (*C*) Superimposed orthodromic responses before (Control) and 30 min PT in the same cell.

Interneuron LTP. Intracellular recordings were carried out in stratum pyramidale, at the border of strata L/M and A/O in the CA1 hippocampal subfield. These interneurons have been identified as GABAergic, mediating synaptic inhibition by a number of previous studies (for review, see ref. 31). Tetanization-induced long-term (>30 min) enhancement of the orthodromic EPSP was observed in 12 of 15 L/M interneurons, in 17 of 26 basket cells, and 11 of 14 A/O interneurons (Table 1).

Twenty of the 55 interneurons that exhibited long-term enhancement of the EPSP (recordings from all three interneuron populations lumped together) fired spontaneously at V_{rest} and 8 of 20 interneurons fired in bursts. Thirty minutes PT, the firing frequency was enhanced in 18 of 20 interneurons. On average, firing frequencies 30 min PT were 14.5 ± 1.3 Hz (spikes per second, mean ± SEM, $n = 7$) in L/M interneurons (up from 11.6 ± 1.4 Hz before tetanus; $P < 0.05$, paired t test), 27.2 ± 2.0 Hz in basket cells (19.5 ± 1.4 Hz before tetanus, $P < 0.05$, $n = 7$), and 18.9 ± 0.8 Hz in A/O interneurons (13.5 ± 2.3 Hz before tetanus, $P < 0.05$, $n = 6$).

LTP: Iontophoretic $GABA_A$ Conductance. Efficacy of $GABA_A$-receptor function during LTP was examined by measuring conductance changes elicited by iontophoretically applied $GABA_A$ agonists muscimol and GABA (Fig. 3). Iontophoretic $GABA_A$ conductance changes could be selec-

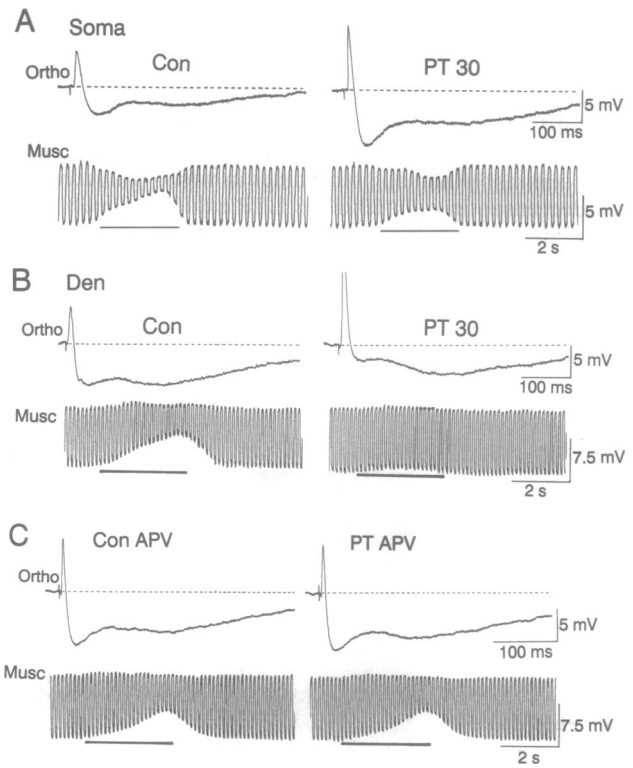

FIG. 3. LTP: Orthodromic potentials and iontophoretic $GABA_A$ responses in CA1 pyramidal cells. (*A*) Soma. Orthodromic responses (upper trace) and responses to iontophoretic muscimol application (eject, +25 nA; retain, −8 nA) (lower trace) before tetanization (Con) and 30 min PT (PT 30) at V_{rest} (−65 mV) (hyperpolarizing current pulses, −0.3 nA and 100 ms; interval, 200 ms). (*B*) Dendrite. Orthodromic and iontophoretic muscimol responses at V_{rest} (−65 mV) before (Con) and 30 min PT. $GABA_A$ conductances [assessed by the responses to hyperpolarizing current pulses (−0.2 nA; duration, 60 ms; interval, 125 ms) during low (+9 nA) muscimol ejecting currents] decreased from 16.42 ± 2.3 nS (mean ± SEM, $n = 3$) before to 1.92 ± 1.2 nS 30 min PT. (*C*) Dendrite. Control, tetanus, and 30 min PT recordings (at V_{rest}, −63 mV) in the presence of D-AP5 (20 μM). Ionotophoretic peak conductances were 12.27 ± 1.9 nS before and 13.33 ± 2.5 nS ($n = 3$) 30 min PT. Muscimol eject current, +5 nA; retain, −8 nA; current pulses, −0.2 nA, 100 ms.

tively (without associated potential changes) elicited by application of low $GABA_A$ agonist ejecting currents (between +5 and +21 nA) (Fig. 3 *B* and *C*). Peak conductance changes were assessed by passing brief pulses of negative current (0.2–0.4 nA, 50–200 ms duration, and 100- to 200-ms intervals) before and during GABA/muscimol application. $GABA_A$ conductance in LTP-exhibiting CA1 pyramidal cell apical dendrites fell from 14.50 ± 1.21 nS (control) to 6.12 ± 0.93 nS (30 min PT) (mean ± SEM; $n = 21$; $P < 0.01$, paired *t* test) (Fig. 3*B*) and in somatic recordings from 14.57 ± 1.4 nS (control) to 9.56 ± 1.3 nS (30 min PT) ($n = 27$; $P < 0.01$, paired *t* test).

LTP: Synaptic $GABA_A$ Conductance. $GABA_A$-mediated membrane conductance increases ("shunting inhibition") rather than summation of hyperpolarizing potentials control excitatory responses in the mammalian central nervous system (24) and large EPSP increases occur upon pharmacological block of $GABA_A$ receptors at the chloride reversal potential (see Fig. 5). Impairment of $GABA_A$-mediated inhibition results in a large enhancement not only of the orthodromic EPSP amplitude but also of the EPSP slope (Fig. 5).

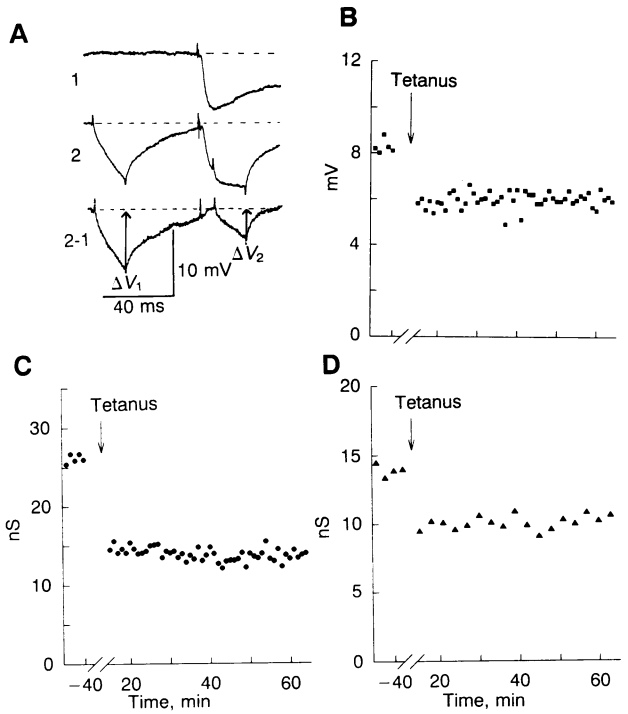

FIG. 4. Tetanization effects on monosynaptic IPSP and synaptic and iontophoretic $GABA_A$ conductance in CA1-pyramidal-cell apical dendrite. Stimulation in stratum radiatum in the presence of CNQX (20 μM), DL-AP5 (100 μM), and saclofen (100 μM) generated monophasic IPSPs at V_{rest} (−63 mV) (in *A*, trace 1). $GABA_A$-mediated synaptic conductances were assessed by hyperpolarizing current pulses ($i = 0.4$ nA, $t = 20$ ms = τ_m) applied at the peak of the monosynaptic IPSP and shortly before the stimulus to assess leak conductance $G(l)$ (trace 2). Trace 2-1 shows the difference of trace 1 substracted from trace 2. With $t = \tau_m$ (assessed by a 300-ms hyperpolarizing current pulse, data not shown), the synaptic conductance [$G(s)$] was calculated by the following formula: $G(s) = i\{1 - \exp[-(\Delta V_1/\Delta V_2)]\}/\Delta V_2 - G(l)$, with $G(l) = i[1 - \exp(-1)]/\Delta V_1$. ΔV_1 and ΔV_2 are amplitudes of membrane potential changes marked by arrows in trace 2-1. A standard tetanus was applied 40 min after washout of CNQX and AP5. Immediately after the tetanus, CNQX and AP5 were reapplied and $GABA_A$-mediated responses [monophasic IPSPs (*B*), synaptic $GABA_A$ conductance (*C*), and iontophoretic $GABA_A$ conductance (*D*)] were measured in the presence of CNQX, AP5, and saclofen. Stimulation responses (IPSPs and synaptic conductances) were evoked every minute and iontophoretic responses were evoked every 3 min.

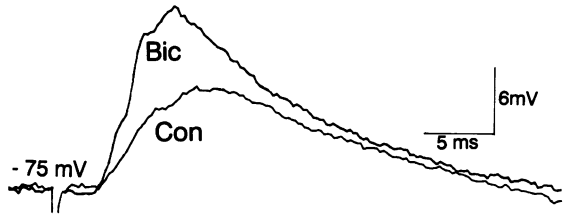

FIG. 5. Pyramidal cell soma recordings at V_{Cl} (−75 mV): orthodromic responses before (Con) and in bicuculline (10 μM, Bic) (superimposed).

The control of the EPSP rising phase by $GABA_A$-mediated inhibition may be due to a combination of activation of a monosynaptic $GABA_A$ component by afferent stimulation (25) (Fig. 4) and fast activation kinetics of $GABA_A$ receptors, in particular conductance increases (24).

Synaptic conductance changes were assessed by brief (15–25 ms) hyperpolarizing current pulses applied at the peak of the monosynaptic IPSP elicited in the presence of CNQX (20 μM), AP5 (100 μM), and saclofen (100 μM) (25) (Fig. 4*A*). Tetanization (applied after restoration of synaptic excitation, see Fig. 4) resulted in significant decreases of synaptic $GABA_A$ conductances: from 21.06 ± 2.46 nS (control) to 9.06 ± 2.08 nS (30 min PT) (mean ± SEM; $n = 9$; $P < 0.001$, paired *t* test). Monosynaptic IPSPs (in the same nine apical dendrites) were reduced from 6.20 ± 0.44 mV (control) to 3.56 ± 0.51 mV (30 min PT) ($P < 0.001$, paired *t* test; $n = 9$). Changes of synaptic conductances and monosynaptic IPSPs correlated with $r = 0.958$. In five apical dendrites, tetanization-induced changes of monosynaptic IPSPs and synaptic conductance were compared with iontophoretically evoked conductance changes (Fig. 4). Changes of tetanization-induced iontophoretic GABA conductances (12.75 ± 0.95 nS, control; 6.9 ± 0.85 nS, 30 min PT; $n = 5$, $P < 0.001$, paired *t* test) correlated with tetanization-induced changes of synaptic $GABA_A$ conductances with $r = 0.930$ and with changes of monosynaptic IPSPs with $r = 0.905$. Changes of synaptic conductances, IPSPs, and iontophoretic conductances correlated with $r = 0.948$.

Role of *N*-Methyl-D-Aspartate Receptors. When the tetanus was applied in the presence of *N*-methyl-D-aspartate-receptor antagonist D-AP5 (10–50 μM), orthodromic EPSPs were unaltered in 8 of 11 somatic and 7 of 9 dendritic recordings 30 min PT (see ref. 32). IPSPs remained unaltered in all 8 somatic and in all 7 dendritic recordings in which the presence of AP5 had prevented lasting EPSP increases after tetanization (Fig. 3*C*). With AP5 present, iontophoretic $GABA_A$ conductances were 16.34 ± 2.5 nS before and 15.83 ± 3.6 nS 30 min PT ($n = 6$; $P > 0.1$, paired *t* test) in pyramidal cell somata and 13.6 ± 4.5 nS before and 11.8 ± 3.4 nS 30 min PT in CA1 apical dendrites ($n = 4$; $P > 0.05$, paired *t* test). Synaptic $GABA_A$ conductances (see Fig. 4) were 22.5 ± 2.5 nS before and 21.4 ± 2.4 nS 30 min PT, respectively, in recordings from CA1 apical dendrites ($n = 4$, $P > 0.1$, paired *t* test). These data indicate that impairment of $GABA_A$-receptor function during LTP is contingent upon *N*-methyl-D-aspartate-receptor activation.

DISCUSSION

Reduction of the strength of synaptic inhibition as an underlying mechanism of enhancement of excitability of cortical populations has been demonstrated in various models of epilepsy (e.g., refs. 33 and 34) including tetanization-induced hyperexcitability (19). With regard to maintenance of LTP, however, the conclusion of several previous studies was that the overall strength of synaptic inhibition is rather enhanced (10–15). Data presented in this report confirm enhancement

of interneuronal output during LTP (Table 1). However, CA1-pyramidal-cell LTP was found to be accompanied by marked impairment of $GABA_A$-receptor function (Figs. 3 *A* and *B* and 4 and Table 1).

What are the functional consequences of opposite changes of synaptic inhibition during LTP in pyramidal cells? With the exception of orthodromic IPSPs in somata [which were variable (Table 1)], all other parameters of $GABA_A$-mediated inhibition (orthodromic IPSPs in dendrites, sIPSPs, and iontophoretic and synaptic $GABA_A$ conductances in both somata and dendrites) were found to be reduced during LTP in the majority of recordings (Figs. 1*C*, 2*B*, 3 *A* and *B*, and 4). These data indicate that disinhibition represents the prevailing mechanism of opposite modifications of synaptic inhibition during LTP.

The variability of changes of the orthodromic early IPSP in somatic recordings during LTP, in particular potentiation in about 40% of recordings (Table 1 and refs. 10–12), served as a main argument against a role of disinhibition as one of the underlying mechanisms of LTP. Potentiated orthodromic IPSPs during LTP are probably the result of tetanization-induced strengthening of interneuronal output since potentiated IPSPs were accompanied by reduced iontophoretic $GABA_A$ conductances in somatic recordings (Fig. 3*A*). Enhanced interneuronal output, in particular of interneurons of the recurrent inhibitory pathway, may lead to a more pronounced strengthening of inhibition in pyramidal cell somata that are densely covered by GABAergic synapses (35). In contrast, impairment of $GABA_A$-receptor function was found to be more prominently expressed at dendritic sites during LTP (see *Results*). Such distinctive subcellular modification of synaptic inhibition in combination with the local action of $GABA_A$-mediated inhibition (36) may underlie the observed somatic–dendritic compartmentalization of orthodromic IPSP changes during LTP. However, the global subcellular enhancement of excitation that originates from a local impairment of synaptic inhibition (e.g., at dendritic sites) (36) can conceivably lead to EPSP potentiation at subcellular sites at which synaptic inhibition is unchanged or even potentiated.

Although a quantitative evaluation of the effects of impaired synaptic inhibition on excitatory responses during LTP remains to be established, the marked increases of excitatory responses that result from a comparable (partial) impairment of $GABA_A$-receptor function in low PTX or bicuculline concentrations are indicative of a critical role of (tetanization-induced) impairment of $GABA_A$-receptor function as underlying mechanism of pyramidal-cell LTP in the CA1 hippocampal subfield.

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