Activation of presynaptic and postsynaptic ryanodine-sensitive calcium stores is required for the induction of long-term depression at GABAergic synapses in the neonatal rat hippocampus.

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Activation of Presynaptic and Postsynaptic Ryanodine-Sensitive Calcium Stores Is Required for the Induction of Long-Term Depression at GABAergic Synapses in the Neonatal Rat Hippocampus

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The role of internal calcium stores in the induction of long-term depression at GABAergic synapses was investigated in the neonatal rat hippocampus. Whole-cell recordings of CA3 pyramidal neurons were performed on hippocampal slices from neonatal (2–4 d old) rats. In control conditions, tetanic stimulation (TS) evoked an NMDA-dependent long-term depression of $GABA_A$ receptor-mediated postsynaptic responses ($LTD_{GABA\text{-}A}$). $LTD_{GABA\text{-}A}$ was prevented when the cells were loaded with ruthenium red, a blocker of Ca^{2+}-induced Ca^{2+} release (CICR) stores, whereas loading the cells with heparin, a blocker of IP_3-induced Ca^{2+} release stores, had no effect. The effects of ryanodine, another compound that interferes with CICR stores, were also investigated. Intracellular injection of ryanodine prevented the induction of $LTD_{GABA\text{-}A}$ only when the TS was preceded by depolarizing pulses that increase intracellular Ca^{2+} concentration. When applied in the bath, ryanodine prevented the induction of $LTD_{GABA\text{-}A}$. Altogether, these results suggest that ryanodine acts as a Ca^{2+}-dependent blocker of CICR stores and that the induction of $LTD_{GABA\text{-}A}$ required the activation of both presynaptic and postsynaptic CICR stores.

Key words: synaptic plasticity; development; GABA; glutamate; calcium stores; hippocampus

In various brain structures, repetitive activation of synaptic connections can lead to a calcium-dependent long-term potentiation (LTP) or long-term depression (LTD) of synaptic transmission, which are held responsible for memory formation or neuronal network development. LTP and LTD are persistent increases or decreases, respectively, in the synaptic strength. In addition to glutamatergic synapses, several recent studies have reported that both LTP and LTD at GABAergic synapses can occur in different brain regions (Kano et al., 1992; Morishita and Sastry, 1993; Komatsu, 1994; Stelzer et al., 1994). Although a postsynaptic rise in intracellular calcium concentration ($[Ca^{2+}]_i$) appears to be the common trigger for inducing synaptic plasticity, the source of calcium and the underlying consequences on synaptic efficacy may differ (Bear and Malenka, 1994; Marty and Llano, 1995; Nicoll and Malenka, 1995). The postsynaptic rise in $[Ca^{2+}]_i$ leading to GABAergic synaptic plasticity can be produced by a calcium entry via NMDA channels (Komatsu and Iwakiri, 1993; Stelzer et al., 1994), by voltage-gated calcium channels (VDCCs) (Kano et al., 1992; Caillard et al., 1999a), or by the release of calcium from $InsP_3$-sensitive internal stores (Komatsu, 1996).

In previous studies (McLean et al., 1996; Caillard et al., 1999b), we have reported that tetanic stimulation of GABAergic and glutamatergic fibers leads to an NMDA-dependent LTD of $GABA_A$ receptor-mediated synaptic transmission ($LTD_{GABA\text{-}A}$). The induction of $LTD_{GABA\text{-}A}$ requires a postsynaptic rise in $[Ca^{2+}]_i$ that is caused, at least in part, by a calcium influx through NMDA channels (Caillard et al., 1999b). The aim of the present study was to investigate the possible contribution of ryanodine-sensitive internal calcium stores (Berridge, 1997) in the induction of $LTD_{GABA\text{-}A}$. We provide evidence that $LTD_{GABA\text{-}A}$ induction requires the activation of both presynaptic and postsynaptic ryanodine-sensitive Ca^{2+} stores.

MATERIALS AND METHODS

Brain slice preparation. Experiments were performed on hippocampal CA3 neurons obtained from postnatal day (P) 2–4 Wistar rats. Brains were removed under cryoanesthesia and submerged in artificial CSF (ACSF) containing (in mM): NaCl 126, KCl 3.5, $CaCl_2$ 2, $MgCl_2$ 1.3, NaH_2PO_4 1.2, $NaHCO_3$ 25, and glucose 11, pH 7.4, when equilibrated with 95% O_2 and 5% CO_2. Hippocampal slices, 600 μM thick, were cut with a McIlwain tissue chopper and incubated in ACSF at room temperature for at least 60 min before use. Individual slices were then transferred to a submerged recording chamber and perfused with ACSF at 2.5–3 ml/min at 34°C.

Whole-cell recordings. Whole-cell recordings were performed with an Axopatch 200B (Axon Instruments) amplifier. The pipette solution contained (in mM): K-gluconate 100, $CaCl_2$ 0.1, EGTA 1.1, HEPES 10, CsCl 20, MgATP 2, $MgCl_2$ 5, cAMP 0.2, NaGTP 0.6, QX314 2, pH_i 7.25, $osmolarity_i$ 275 mOsm. In some experiments, heparin (2 mg/ml), ryanodine (10 μM), or ruthenium red (20 μM) was dissolved in the pipette solution. Capacitance and membrane resistance were determined by an online fitting analysis of the transient currents in response to a 5 mV pulse with Acquis Software (ACQUIS, G. Sadoc, Bio-Logic). Compensation parameters were set to 50–70%. Cells recorded with unstable membrane resistance or series resistances were discarded.

Received Feb. 23, 2000; revised May 22, 2000; accepted June 19, 2000.

This work was supported by the Institut National de la Santé et de la Recherche Médicale. Olivier Caillard was supported by a grant from the Ministère de l'Enseignement Supérieur et de la Recherche.

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This article is published in *The Journal of Neuroscience*, Rapid Communications Section, which publishes brief, peer-reviewed papers online, not in print. Rapid Communications are posted online approximately one month earlier than they would appear if printed. They are listed in the Table of Contents of the next open issue of JNeurosci. Cite this article as: JNeurosci, 2000, 20:RC94 (1–6). The publication date is the date of posting online at www.jneurosci.org.

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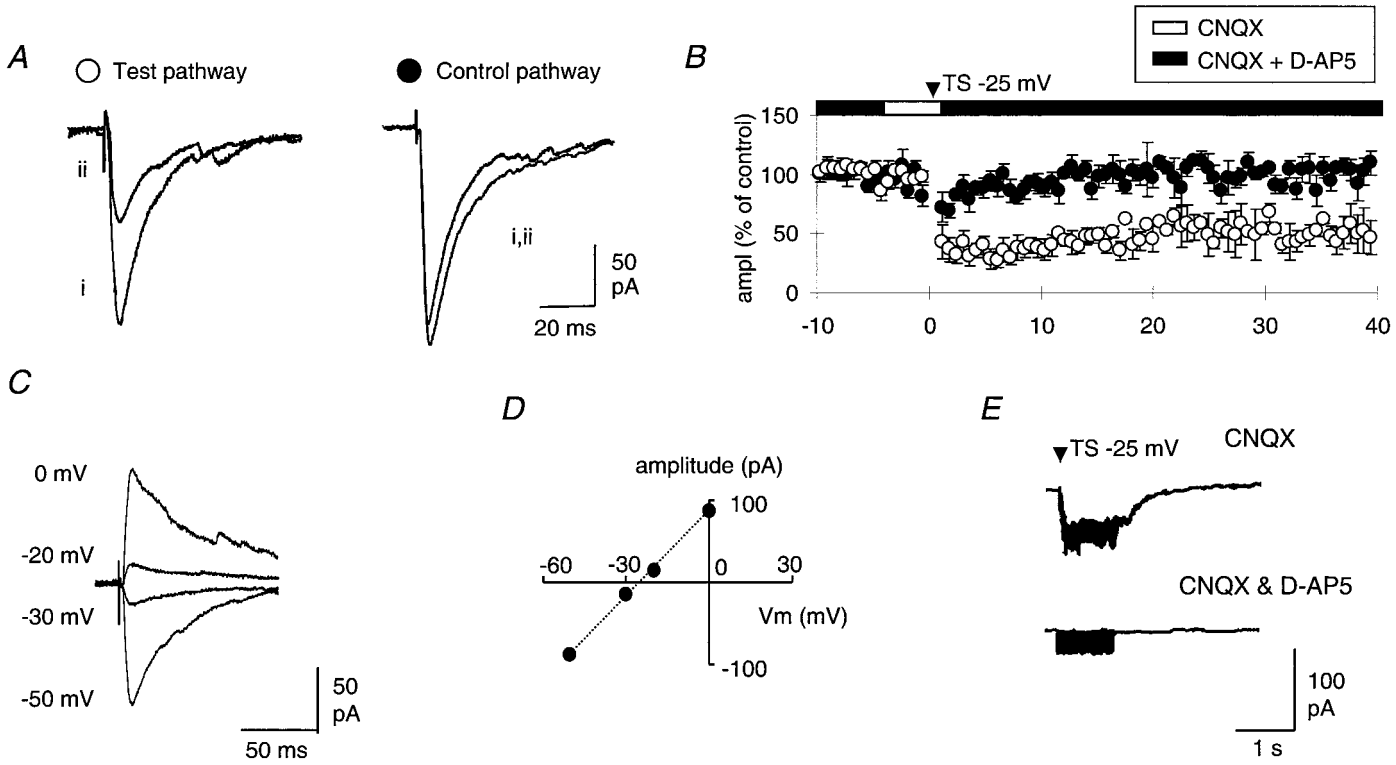

Figure 1. Tetanic stimulation induced $LTD_{GABA\text{-}A}$. *A*, Superimposed averaged $GABA_A$ PSCs ($n = 5$) of the test and control pathway recorded in CNQX (10 μM) and D-AP5 (50 μM) before (*i*) and 20 min after (*ii*) TS. TS was applied to the test pathway at a depolarized holding potential (−25 mV) in the presence of CNQX. *B*, Time course of changes in the $GABA_A$ PSCs amplitude presented as a percentage of pretetanized amplitude on the test (○) and control (●) pathway ($n = 7$). *C*, Superimposed averaged $GABA_A$ PSCs ($n = 5$) recorded in CNQX (10 μM) and D-AP5 (50 μM) at different holding membrane potentials. *D*, *I–V* curve of the averaged $GABA_A$ PSCs shown in *A*. The reversal potential for $GABA_A$ PSCs is −25 mV. *E*, TS-induced inward currents in CNQX and CNQX + D-AP5 recorded at the reversal potential of $GABA_A$ PSCs.

Electrical stimulation (30–60 μsec, 10–30 V, 0.03 Hz) of a test and a control pathway was performed with two bipolar tungsten electrodes located in the stratum radiatum on both sides of the recording electrode. Three tetanic stimuli (100 Hz, 1 sec, 30 sec intervals) were delivered to the test pathway. Tetanic stimulation (TS) was applied between 10 and 12 min after the seal was broken. The intensity of test and tetanic stimuli was two to three times the threshold required to elicit $GABA_A$-mediated responses.

Data acquisition, analysis, and drugs. Evoked $GABA_A$ receptor-mediated synaptic responses were stored on a personal computer for subsequent analysis (ACQUIS, G. Sadoc, Bio-Logic). To rule out possible rundown of GABAergic responses, the amplitude of the test $GABA_A$-mediated responses was compared with the control pathway. For data presented as the mean ± SEM, statistical analysis was performed using a Student's paired *t* test. Statistical analysis of percentage values was performed with ANOVA tests. Data were judged to differ when $p < 0.05$. 6-Cyano-7-nitroquinoxaline-2,3-dione (CNQX), D(−)2-amino-5-phosphovaleric acid (D-AP5), and QX314 were purchased from Tocris Cookson. Heparin, ryanodine, and ruthenium red were purchased from LC Laboratories.

RESULTS

The protocol used to test the effect of tetanic stimulation on GABAergic synaptic efficacy was the following (Fig. 1). Two independent afferent pathways (control and test) were stimulated alternately to evoke $GABA_A$ receptor-mediated postsynaptic currents ($GABA_A$ PSCs) at a holding potential of −60 mV (Fig. 1*A*). After a control period, D-AP5 was washed out, and three TSs (100 Hz, 1 sec, three times, 30 sec interval) were delivered to the test pathway in the presence of CNQX (10 μM) alone at a depolarized holding potential ranging from −30 to −25 mV (Fig. 1*B*). At this potential, which corresponds to the reversal potential of $GABA_A$ PSCs with our recording solution (Fig. 1*C*,*D*), the voltage-dependent blockade of NMDA channels by Mg^{2+} is alleviated (Nowak et al., 1984). This procedure allowed us to measure the NMDA receptor-mediated current induced by TS (Fig. 1*E*). As already reported in our previous study (Caillard et al., 1999b), TS produced an NMDA receptor-mediated inward current of −43 ± 9 pA and induced a robust homosynaptic $LTD_{GABA\text{-}A}$ (Fig. 1*A*,*B*): the average amplitude of the test $GABA_A$ PSCs was 49 ± 11% of the control pathway 40 min after TS ($p < 0.01$, $n = 10$).

$LTD_{GABA\text{-}A}$ induction requires the activation of postsynaptic Ca^{2+} induced-Ca^{2+} release stores

To investigate the possible contribution of internal calcium stores to the induction of $LTD_{GABA\text{-}A}$, cells were loaded with heparin, a blocker of $InsP_3$ induced-Ca^{2+} release (IICR) stores (Berridge, 1993), or ruthenium red, a blocker of Ca^{2+} induced-Ca^{2+} release (CICR) stores (Nagasaki and Fleischer, 1989). In cells loaded with heparin (2 mg/ml), TS applied at −30 ± 1 mV produced an average inward current of −60 ± 5 pA ($n = 7$, $p = 0.14$ when compared with control) and generated a homosynaptic $LTD_{GABA\text{-}A}$ (Fig. 2*A*,*B*): the average amplitude of test $GABA_A$ PSCs was 47 ± 6% of the control pathway 40 min after TS ($p < 0.01$, $n = 7$). In cells loaded with ruthenium red (20 μM), TS applied at −29 ± 2 mV induced an average inward current of −49 ± 6 pA ($n = 6$, $p = 0.60$ when compared with control) but failed to induce a homosynaptic $LTD_{GABA\text{-}A}$ (Fig. 2*C*,*D*): the average amplitude of test $GABA_A$ PSCs was 93 ± 5% of the control pathway 40 min after TS ($p = 0.20$, $n = 6$). These results therefore suggest that the activation of postsynaptic CICR stores but not postsynaptic IICR is required for the induction of $LTD_{GABA\text{-}A}$.

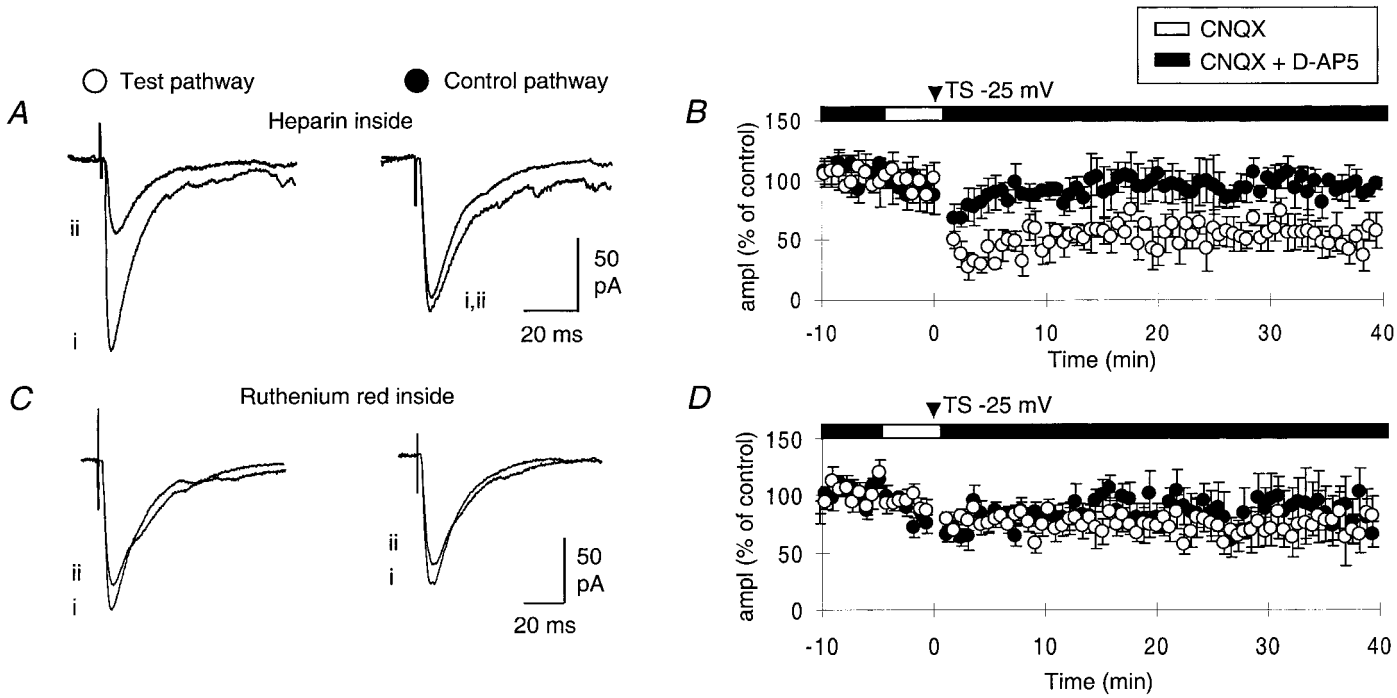

Figure 2. Release of calcium from postsynaptic CICR is required for the induction of $LTD_{GABA\text{-}A}$. *A*, Superimposed averaged $GABA_A$ PSCs ($n = 5$) of the test and control pathway recorded in CNQX (10 μM) and D-AP5 (50 μM) before (*i*) and 20 min after (*ii*) TS. TS was applied to the test pathway at a depolarized holding potential (−25 mV) in the presence of CNQX. *B*, Time course of changes in the $GABA_A$ PSCs amplitude presented as a percentage of pretetanized amplitude on the test (○) and control (●) pathway ($n = 7$). In *A* and *B*, the pipette solution contained heparin (2 mg/ml). *C*, *D*, Same as in *A* and *B* except that the pipette solution contained ruthenium red (20 μM).

$LTD_{GABA\text{-}A}$ induction requires the activation of postsynaptic ryanodine-sensitive calcium stores

To further demonstrate the involvement of postsynaptic CICR in the induction of $LTD_{GABA\text{-}A}$, cells were loaded with ryanodine (10 μM) to block CICR (Nagasaki and Fleischer, 1988; Berridge and Dupont, 1994). Because previous studies have suggested that ryanodine required a rise in $[Ca^{2+}]_i$ to efficiently interfere with CICR (Kano et al., 1995), the following protocols were designed. In a first set of experiments, ryanodine-loaded cells were recorded in voltage-clamp mode. In a second set of experiments, cells were recorded in current-clamp mode, and 10 depolarizing current pulses (50 msec duration, 0.03 Hz, one to three action potentials per pulses) (Fig. 3*C–E*, *inset*) were applied during the control period to activate the VDCCs. We hypothesized that clamping the cells at a hyperpolarized potential will prevent postsynaptic calcium influx, thus preventing the effect of ryanodine, whereas under current-clamp mode, the activation of VDCCs will allow ryanodine to efficiently act on postsynaptic CICR.

In ryanodine-loaded cells recorded in voltage-clamp mode ($V_h = -60$ mV), TS produced an inward current of -45 ± 7 pA at -25 ± 1 mV ($n = 7, p = 0.84$ when compared with control) and generated a homosynaptic $LTD_{GABA\text{-}A}$ (Fig. 3*A*,*B*): the average amplitude of test $GABA_A$ PSCs was 55 ± 6% of the control pathway 40 min after TS ($p < 0.01$, $n = 7$). In current-clamp experiments, however, when VDCCs were activated during the control period to allow postsynaptic Ca^{2+} influx, postsynaptic infusion of ryanodine prevented the induction of $LTD_{GABA\text{-}A}$. Thus, in control cells TS induced a membrane depolarization of 21 ± 3 mV and a homosynaptic $LTD_{GABA\text{-}A}$ (Fig. 3*C*,*D*): the average amplitude of test $GABA_A$ PSPs was 48 ± 5% of the control pathway 40 min after TS ($p < 0.01$, $n = 7$). In ryanodine-loaded cells, although the amplitude of the TS-induced membrane depolarization was similar to control (20 ± 3 mV, $p = 0.74$), TS failed to induce an $LTD_{GABA\text{-}A}$ (Fig. 3*E*,*F*): the average amplitude of test $GABA_A$ PSPs was 106 ± 5% of the control pathway 40 min after TS ($p = 0.23, n = 6$). The latter experiment was also performed in voltage-clamp mode ($n = 2$). Under these conditions, the application of depolarizing voltage steps to ryanodine-loaded cells also prevented the induction of $LTD_{GABA\text{-}A}$ (data not shown).

These results therefore suggested that ryanodine acts as a Ca^{2+}-dependent blocker of CICR stores and confirmed that postsynaptic ryanodine-sensitive calcium stores are involved in the induction of $LTD_{GABA\text{-}A}$.

$LTD_{GABA\text{-}A}$ induction requires the activation of presynaptic ryanodine-sensitive calcium stores

Having established that ryanodine required a postsynaptic rise in $[Ca^{2+}]_i$ to act on CICR, we thought to test the effect of bath-applied ryanodine to investigate the contribution of presynaptic CICR. We reasoned that under voltage-clamp recording, bath-applied ryanodine, which permeates both presynaptic and postsynaptic membranes, will only act at presynaptic levels because spontaneous and evoked activities triggered by presynaptic calcium rises are present. When ryanodine (10 μM) was applied by bath during the washout of D-AP5, it prevented the induction of $LTD_{GABA\text{-}A}$ (Fig. 4*A*,*B*): the average amplitude of test $GABA_A$ PSCs was 108 ± 8% of the control pathway 40 min after TS ($p = 0.22$, $n = 5$). In this condition, the amplitude of the inward current induced by TS was similar to that evoked in control conditions (-48 ± 6 pA at -26 ± 1 mV, $n = 7, p = 0.77$ when compared with control).

Altogether, the observation that ryanodine prevented $LTD_{GABA\text{-}A}$ when applied in the bath but not when loaded into the recorded cell unless a postsynaptic rise in $[Ca^{2+}]_i$ was induced suggested that presynaptic CICR stores were required for the induction of $LTD_{GABA\text{-}A}$.

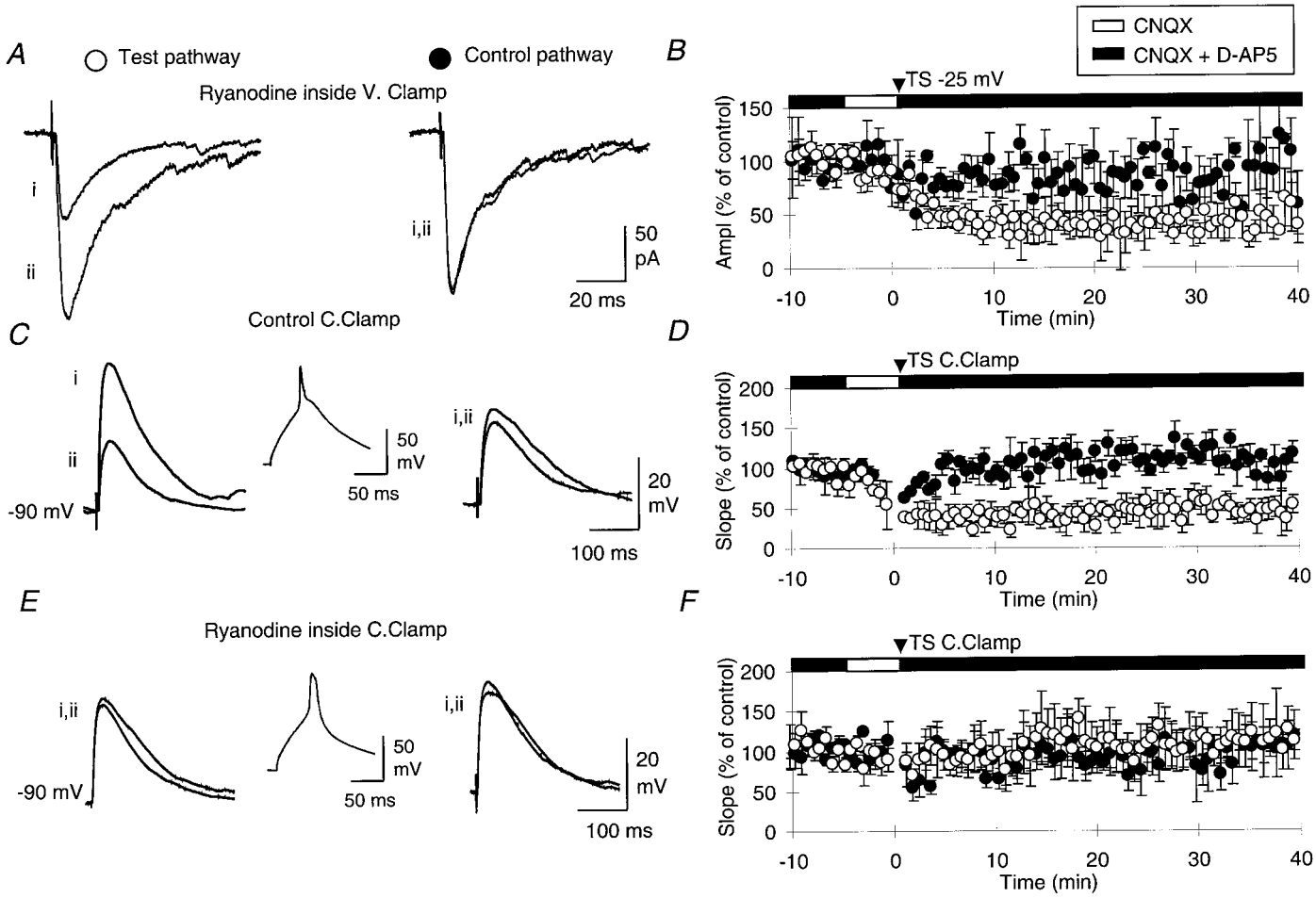

Figure 3. Ryanodine requires a rise in $[Ca^{2+}]_i$ to act on CICR. *A*, Superimposed averaged $GABA_A$ PSCs ($n = 5$) of the test and control pathway recorded in CNQX (10 μM) and D-AP5 (50 μM) before (*i*) and 20 min after (*ii*) TS in ryanodine-loaded cells. TS was applied to the test pathway at a depolarized holding potential (−25 mV) in the presence of CNQX. *B*, Time course of changes in the $GABA_A$ PSCs amplitude presented as a percentage of pretetanized amplitude on the test (○) and control (●) pathway ($n = 7$). *C*, Superimposed averaged $GABA_A$ PSPs ($n = 5$) of the test and control pathway recorded in CNQX (10 μM) and D-AP5 (50 μM) before (*i*) and 20 min after (*ii*) TS. TS was applied to the test pathway at a depolarized membrane potential (−25 mV) in the presence of CNQX. The *middle trace* shows the response to a depolarizing current step (50 msec, 250 pA) given during the control period (0.03 Hz). *D*, Time course of changes in the $GABA_A$ PSPs amplitude presented as a percentage of pretetanized amplitude on the test (○) and control (●) pathway ($n = 7$). *E*, *F*, Same as in *A* and *B* except that the cells were loaded with ryanodine (10 μM).

DISCUSSION

The results presented here provide evidences that $LTD_{GABA\text{-}A}$ induction requires the activation of both presynaptic and postsynaptic ryanodine-sensitive calcium stores.

$LTD_{GABA\text{-}A}$ induction requires the activation of postsynaptic CICR

Our conclusion that postsynaptic stores are involved in the induction of $LTD_{GABA\text{-}A}$ is supported by the fact that loading the recorded neurons with ruthenium red or ryanodine (provided that a postsynaptic calcium rise occurred; see below) (Berridge and Dupont, 1994) prevents the induction of $LTD_{GABA\text{-}A}$. In ruthenium red- or ryanodine-loaded cells, the amplitude of the inward current or membrane depolarization generated by TS did not differ from that induced in control conditions, thus ruling out unspecific effects on postsynaptic NMDA receptors, which must be activated for the induction of $LTD_{GABA\text{-}A}$ (Caillard et al., 1999b). Several studies have reported that although spatially distinct, IICR and CICR stores can interact mutually. For instance, ryanodine was shown to empty IP3-sensitive pools in CA1 pyramidal neurons (Nakamura et al., 1999) and cerebellar Purkinje cells (Khodakhah and Armstrong, 1997). As such, the preventive effect of ryanodine may be accounted for by the interaction with IICR. This hypothesis appears extremely unlikely, however, because ruthenium red, a blocker of CICR that does not interact with IICR, also prevented the induction of $LTD_{GABA\text{-}A}$.

In a previous study we reported that the induction of $LTD_{GABA\text{-}A}$ requires a postsynaptic increase in $[Ca^{2+}]_i$, provided by an influx of calcium through NMDA channels (Caillard et al., 1999b). The present results suggest that this signal has to be magnified by calcium release from CICR to induce $LTD_{GABA\text{-}A}$. A postsynaptic amplification of an NMDA channel-mediated rise in $[Ca^{2+}]_i$ that may play an inductive role in LTD of glutamatergic synaptic transmission (Reyes and Stanton, 1996) has been reported in the adult hippocampus (Segal and Manor, 1992; Alford et al., 1993; Emptage et al., 1999). In the visual cortex, LTP of GABAergic synaptic transmission involves the activation of IICR stores (Komatsu, 1996). There are also suggestions that IICR stores may be involved in the induction of glutamatergic LTD in the cerebellum (Daniel et al., 1998) and CA1 hippocampal region (Reyes and Stanton, 1996). In the present study, we have shown that loading the cells with heparin does not prevent the induction of $LTD_{GABA\text{-}A}$. However, because we cannot exclude an inefficient dialysis of the recorded cell, the possible

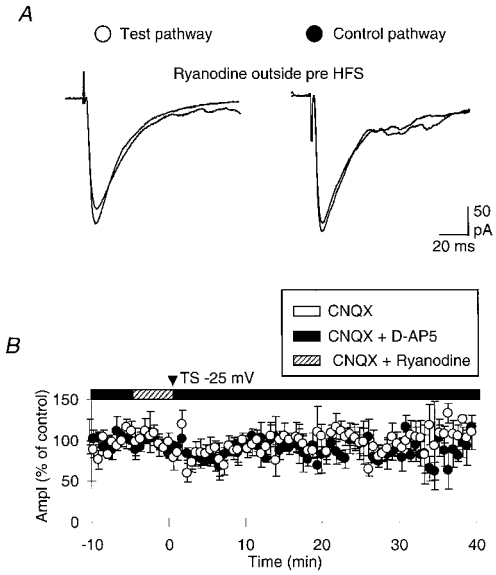

Figure 4. Activation of presynaptic ryanodine-sensitive calcium stores is required for the induction of $LTD_{GABA\text{-}A}$. *A*, Superimposed averaged $GABA_A$ PSCs ($n = 5$) of the test and control pathway recorded in CNQX (10 μM) and D-AP5 (50 μM) before (*i*) and 20 min after (*ii*) TS. TS was applied to the test pathway at a depolarized holding potential (−25 mV) in the presence of CNQX and ryanodine (10 μM). *B*, Time course of changes in the $GABA_A$ PSCs amplitude presented as a percentage of pretetanized amplitude on the test (○) and control (●) pathway ($n = 7$).

contribution of the IICR stores remains questioned. Although we cannot completely exclude the involvement of IICR stores, our results show that the activation of postsynaptic CICR is necessary to reach the postsynaptic $[Ca^{2+}]_i$ threshold required to trigger $LTD_{GABA\text{-}A}$.

$LTD_{GABA\text{-}A}$ induction requires the activation of presynaptic CICR

There are some suggestions regarding the involvement of presynaptic CICR stores in the induction of synaptic plasticity. Thus, calcium-sequestering ability associated with the endoplasmic reticulum is present on presynaptic nerve terminals (Hartter et al., 1987; Finch et al., 1991; Sharp et al., 1993), and a possible contribution of presynaptic stores in the induction of LTD at glutamatergic hippocampal synapses has been reported (Reyes and Stanton, 1996). The suggestion that the activation of presynaptic ryanodine-sensitive calcium stores is also required for the induction of $LTD_{GABA\text{-}A}$ is based on the observation that bath application of ryanodine, which permeates both presynaptic and postsynaptic membranes, did block the induction of $LTD_{GABA\text{-}A}$, whereas a postsynaptic infusion did not unless postsynaptic rises in calcium were induced before TS. The latter is likely attributable to a calcium-dependent action of ryanodine on CICR (Kano et al., 1995) and not to an inefficient dialysis of the recorded cells, because in all experiments (with or without postsynaptic rises in calcium) TS was delivered within 10 to 12 min after breaking the seal. Furthermore, ryanodine did not alter the TS-induced postsynaptic responses, showing that NMDA-mediated responses were not affected.

We interpret our results, taken all together, as follows. In voltage-clamp experiments, the postsynaptic cell is held at a hyperpolarized potential. In this condition, no postsynaptic rise in calcium occurred, thus preventing the effects of ryanodine on CICR either applied to the bath or into the recorded cell. However, at the presynaptic level, calcium rise do occur, as revealed by the presence of both spontaneous and evoked activities, and bath-applied ryanodine could efficiently deplete presynaptic CICR, thus preventing the induction of $LTD_{GABA\text{-}A}$.

Conclusion

In summary, we have provided evidence that the induction of $LTD_{GABA\text{-}A}$ required the activation of postsynaptic and presynaptic ryanodine-sensitive calcium stores. Further experiments are required to clarify the mechanisms leading to the activation of presynaptic ryanodine-sensitive calcium stores. In a previous study we have shown that $LTD_{GABA\text{-}A}$ is homosynaptic and likely expressed presynaptically as a decrease in quantal content (Caillard et al., 1999b). The presynaptic ryanodine-sensitive calcium stores could therefore have a permissive role and act in synergy with the actions of a putative retrograde messenger released from the postsynaptic site. This latter hypothesis may explain why $LTD_{GABA\text{-}A}$ is expressed only at tetanized fibers.

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