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ORIGINAL ARTICLE

GABAergic Interneurons are Required for Generation of Slow CA1 Oscillation in Rat Hippocampus

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Abstract Neuronal oscillations are fundamental to hippocampal function. It has been shown that GABAergic interneurons make an important contribution to hippocampal oscillations, but the underlying mechanism is not well understood. Here, using whole-cell recording in the complete hippocampal formation isolated from rats at postnatal days 14–18, we showed that $GABA_A$ receptor-mediated activity enhanced the generation of slow CA1 oscillations. *In vitro*, slow oscillations (0.5–1.5 Hz) were generated in CA1 neurons, and they consisted primarily of excitatory rather than inhibitory membrane-potential changes. These oscillations were greatly reduced by blocking $GABA_A$ receptor-mediated activity with bicuculline and were enhanced by increasing such activity with midazolam, suggesting that interneurons are required for oscillation generation. Consistently, CA1 fast-spiking interneurons were found to generate action potentials usually preceding those in CA1 pyramidal cells. These findings indicate a $GABA_A$ receptor-based mechanism for the generation of the slow CA1 oscillation in the hippocampus.

Keywords Hippocampus · Oscillation · Synchronization · GABAergic interneuron · $GABA_A$ receptor

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Introduction

Neuronal oscillations in the hippocampus are critical for its functions such as learning and memory [1–5]. Elucidating the neuronal mechanisms responsible for the generation and propagation of oscillations in hippocampal networks is there fore an important issue for understanding hippocampus-dependent functions. Previous studies have shown that a network oscillation depends on the interaction between pyramidal cells (PCs) and GABAergic interneurons [6–9]. In network connectivity, it is known that GABAergic interneurons receive converging inputs from multiple PCs, and make widespread synaptic arborizations on PCs as well as connections with other interneurons *via* both chemical and electrical synapses [7, 10, 11]. Owing to this principal feature, GABAergic interneurons are thought to be capable of coordinating neuronal activity to produce oscillatory activity and network synchronization [12–14]. In studies of the hippocampus, early electrophysiological recording *in vitro* demonstrated that a single interneuron can synchronize the excitatory activity of a large number of PCs, due to the interaction of $GABA_A$-receptor-mediated perisomatic hyperpolarization with intrinsic oscillatory mechanisms in PCs [8]. More recent *in vitro* studies with electrophysiological recording or dynamic imaging have further provided unambiguous evidence that GABAergic interneurons coordinate excitatory activity and generate neuronal oscillations, for example, as demonstrated by stimulating GABAergic "hub" neurons, a super-connected "node" that has a long axon running parallel to the cell layer and innervates widely-distributed PCs in the dentate gyrus and CA1 region [15–17]. The contribution of GABAergic interneurons to hippocampal oscillations has also been investigated recently *in vivo*. In attempts to manipulate the activity of interneurons by selectively knocking out different subunits of glutamatergic

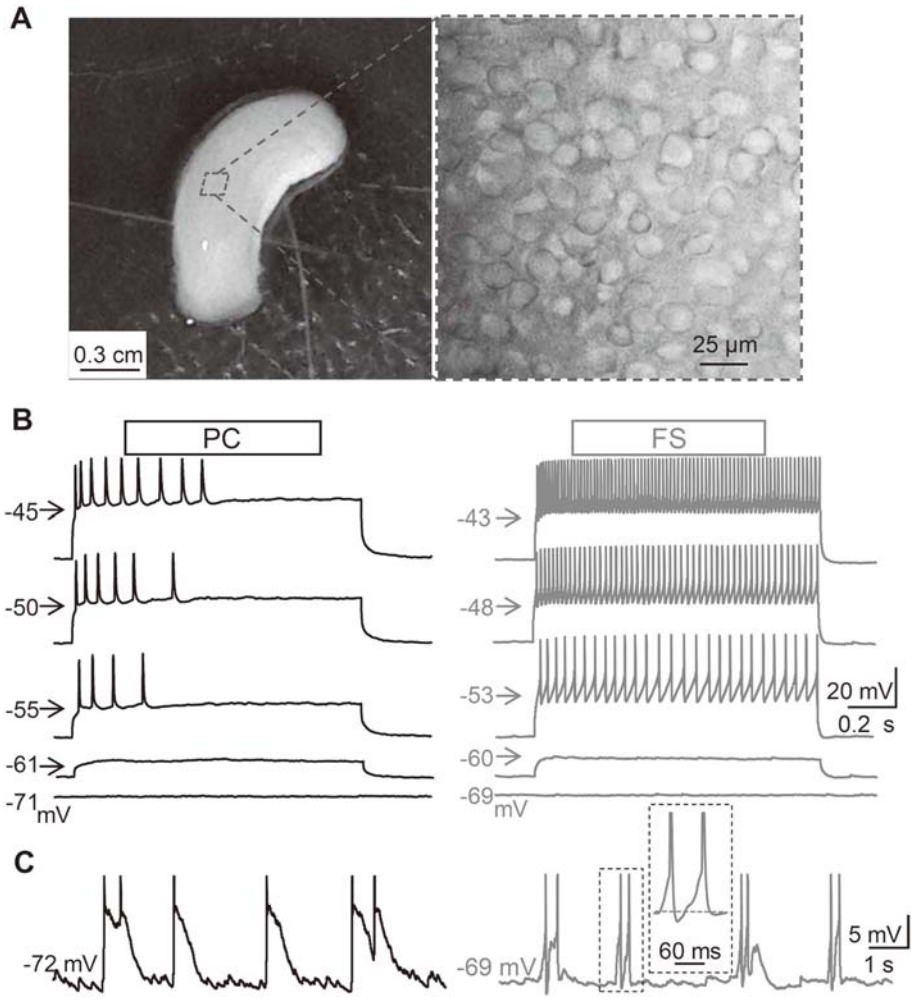

Fig. 1 Complete hippocampal formation *in vitro* and whole-cell recordings from CA1 PCs and FS cells. **A** Left, image of a completely isolated rat hippocampus (scale bar, 0.3 cm); right, image of the CA1 cell layer (scale bar, 25 μm; top view). **B** Representative recordings displaying the low firing rates with adaptation in a pyramidal cell (PC) and sustained firing at high rates in a fast-spiking (FS) cell recorded at depolarizing potentials indicated by arrows. Recordings were performed in the presence of the AMPAR antagonist DNQX (20 μmol/L). **C** For the two cells shown in B (before DNQX application), spontaneous membrane-potential changes and firing of the PC (left) and FS cell (right; inset, high temporal resolution of the fast afterhyperpolarization after the end of action potentials). Resting potentials are indicated on the left of each trace; action potentials were partially truncated.

and GABAergic receptors in interneurons, alterations in hippocampal theta, gamma, and ripple oscillations have been found [18–21]. Cell type-specific manipulations based on optogenetics have on the other hand provided *in vivo* evidence that GABAergic interneurons control oscillatory activity in hippocampal PCs, as shown by changes in theta [22, 23] and ripple rhythms [24]. In this study, we made whole-cell recordings on CA1 neurons of a completely isolated hippocampus, in which slow oscillations could be generated intrinsically in hippocampal neurons, to investigate the contribution of GABAergic interneurons to hippocampal generation of neuronal oscillation.

Materials and Methods

Preparation of Complete Hippocampus and Electrophysiology

We used Sprague-Dawley rats on postnatal days 14 to 18. This study was approved by the Animal Care and Use Committee of East China Normal University (Publication NDGZ-01, revised in 2012). Animals were anaesthetized with pentobarbital (intraperitoneally, 80 mg/kg; Sigma), and after decapitation the brain was rapidly removed and placed in ice-cold artificial cerebrospinal fluid (aCSF, which contained (in mmol/L) 119 NaCl, 2.5 KCl, 2.5 $CaCl_2$, 1.3 $MgSO_4$, 1 NaH_2PO_4, 26.2 $NaHCO_3$, and 11 glucose) for 1 min. Then the brain was placed on a glass plate, which could be rotated on an ice plate and used for the following dissection. The two hemispheres were separated with razor blades. The tissue beneath the cortex and hippocampus was removed by pulling away the cerebellum, brainstem, and thalamus to expose the hippocampal formation. The hippocampus was separated from the surrounding cortical issue with a small metal hook, by carefully pulling the dorsal hippocampus in the caudal direction. Any remaining tissue and blood vessels surrounding the hippocampal formation were gently removed with micro-scissors and brushes. These dissection procedures are similar to those in a study reported by another group [25], and were completed within 0.5–1 min. The

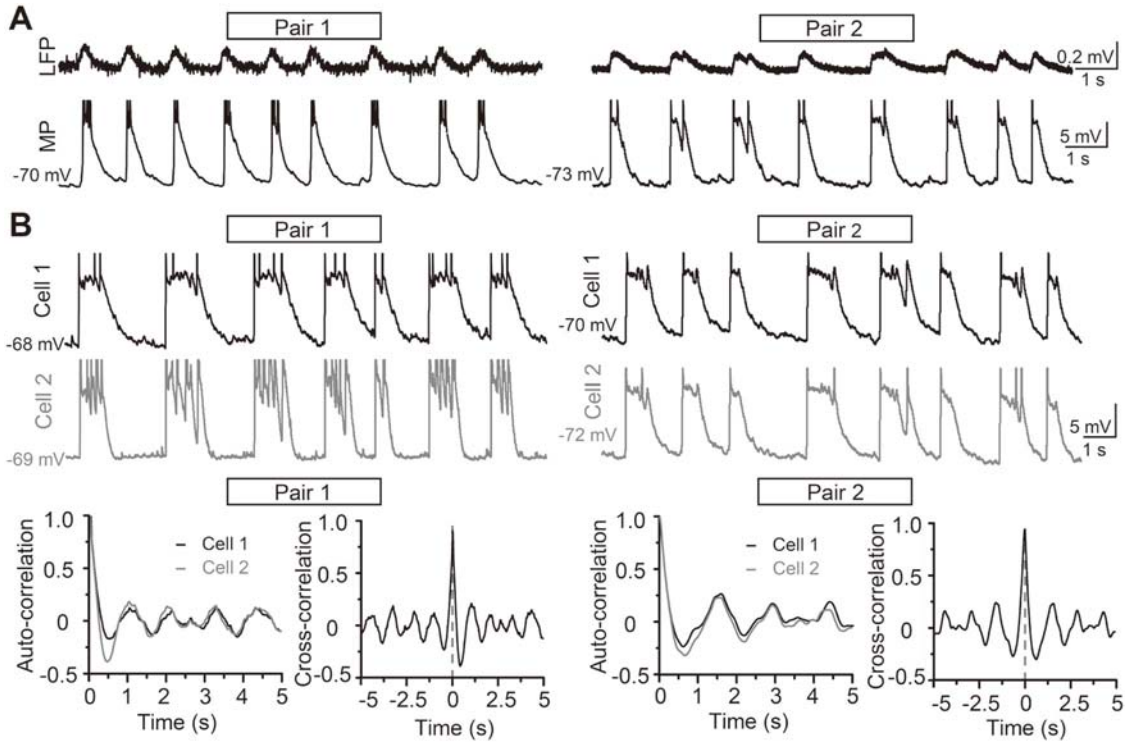

Fig. 2 Oscillatory V_m depolarizations intrinsically generated in CA1 PCs of the complete hippocampus *in vitro*. **A** Two pairs (Pairs 1 and 2) of CA1 local field potential (LFP) recordings (upper traces) and whole-cell recordings from CA1 PCs (lower traces; action potentials were partially truncated) showing spontaneously-occurring oscillatory depolarizations that were phase-locked to LFP changes. **B** Two pairs of whole-cell recordings from CA1 PCs showing synchronized oscillations. Upper, raw traces; lower, auto-correlograms for the oscillations of individual PCs and cross-correlograms for the synchronization between V_m changes.

complete hippocampus was then incubated in aCSF at room temperature for >1 h before electrophysiological recording, and was used within 6 h after dissection.

The recording temperature in the submerged chamber was maintained at 28–30°C. Neurons were visualized with an Olympus microscope (DX50WI, Tokyo, Japan) using infrared video and differential interference contrast optics (Fig. 1A). Perforated whole-cell recordings were made using a procedure similar to that described previously [26]. Patch pipettes with a tip opening of 2.5–3.0 μm were pulled from borosilicate glass tubing (Kimble Glass Inc., Querétaro, Mexico), and had resistances of 3.0–4.5 MΩ. The internal solution contained (in mmol/L) 136.5 K-gluconate, 17.5 KCl, 9.0 NaCl, 1.0 $MgCl_2$, 10.0 HEPES, 0.2 EGTA, and amphotericin B (0.3 mg/mL); small amounts (0.5–0.8 mg/mL) of glass beads (5–15 μm in diameter; Polysciences, Inc., Warrington, UK) were included to allow precipitate-free solution into the pipette tip. Patch pipettes filled with aCSF were used for local field potential (LFP) recording. The recording pipette was advanced into the hippocampus with a motor-driven manipulator (Siskiyou MMX7630, Siskiyou Corp., Grants Pass, OR). Signals were acquired with patch-clamp amplifiers (Axopatch 700B, Axon Instruments, CA) and sampled at 5 kHz by a data acquisition card (Digidata 1440, Axon Instruments), with a 2 or 5 kHz low-pass filter.

Recordings were made from CA1 PCs in the cell layer and fast-spiking (FS) cells in the stratum oriens. Low firing rates with adaptation were recorded in PCs and sustained firing at high rates in FS cells (Fig. 1B). In addition, their spike half-widths were distinct (PCs, 3.1 ± 0.6 ms; FS cells, 1.5 ± 0.3 ms), and in FS neurons, a fast afterhyperpolarization (AHP) was seen immediately after the action potential (Fig. 1C).

Liquid junction potentials (–13 mV) were corrected. Recordings with resting potentials between –65 mV and –75 mV were included for further analysis. The series resistance (uncompensated) was 48 ± 15 MΩ.

Slice Preparation and Electrophysiology

Rats at the same age as those for the complete hippocampus were used for cutting hippocampal slices. Animals were initially anaesthetized with sodium pentobarbital, and after decapitation the brain was rapidly removed and placed in ice-cold aCSF (the same as for the complete

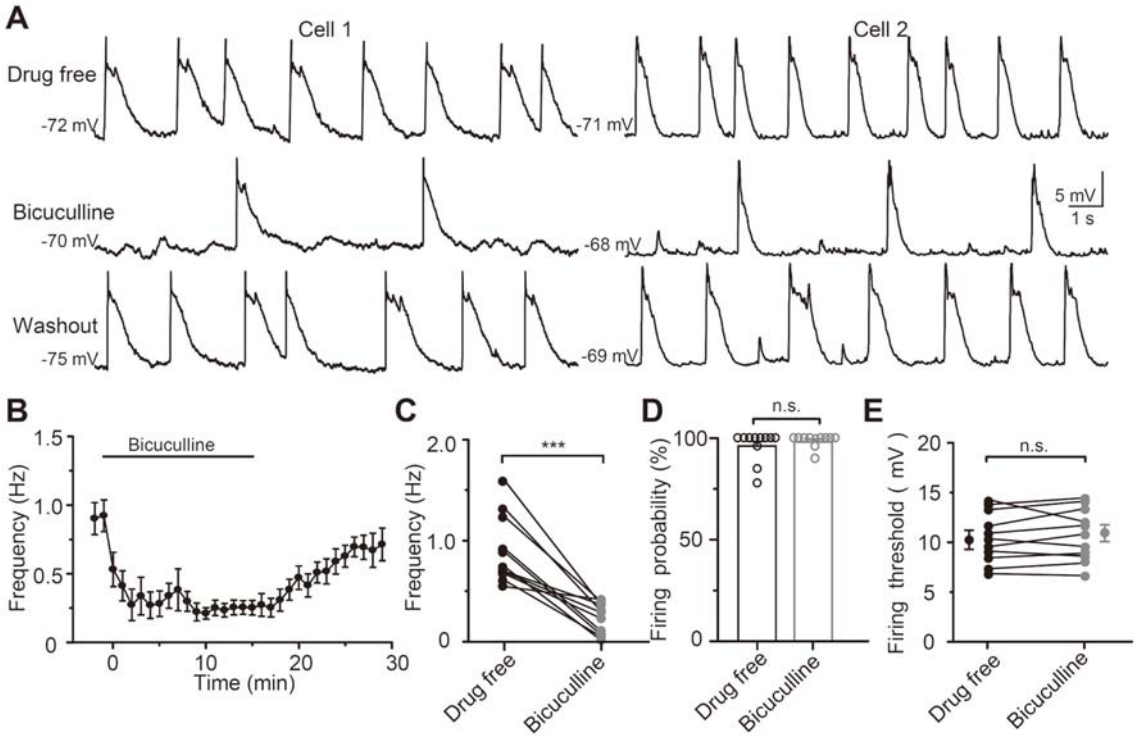

Fig. 3 Blocking $GABA_A$ receptors with bicuculline diminished the intrinsically entrained oscillations in CA1 PCs. **A** Two example recordings (from different hippocampal formations) from CA1 PCs showing oscillations in the absence and presence of bicuculline. **B** For all experiments such as those in A (n = 11), time-course plots for the changes (averaged across the population data) in the frequency of oscillations induced by bicuculline. Time 0 indicates the beginning of drug application. **C–E** Oscillation frequencies (C; dots connected by lines, data from the same cell), firing probability of oscillatory V_m depolarization (D; dots, individual data; histograms, mean ± SEM), and firing thresholds (E; from resting potentials; dots with bars, mean ± SEM) for all cells shown in B. Data were measured 0–2 min before and 10–15 min after drug application. ***$P < 0.001$; n.s., not significant.

hippocampus). Coronal slices (400 μm thick) containing the dorsal hippocampus were cut on a vibratome (Leica VT1000 S, Wetzlar, Germany), and were then incubated at room temperature for >1 h before electrophysiological experiments. Recording temperature in the submerged chamber was maintained at 28–30°C. Perforated whole-cell recordings from CA1 PCs were made as for the complete hippocampus. Bipolar tungsten electrodes were placed in the stratum radiatum for stimulation, which was produced by a pulse generator (Master-8; AMPI, Jerusalem, Israel) through a stimulus isolator (ISO-Flex; AMPI). Excitatory postsynaptic potentials (EPSPs) were evoked at 0.17 Hz.

Data Analysis and Statistics

Firing thresholds were defined as the membrane potential (V_m) value at which dV/dt was >10 V/s. Unless otherwise specified, statistical significance was determined using the paired Student's t-test, and average values are presented as mean ± SEM.

Results

Intrinsically Generated Oscillatory Membrane Potential Depolarizations in CA1 Neurons of the Complete Hippocampus *in Vitro*

We used the complete hippocampus isolated from 14–18 day-old rats to examine the contribution of GABAergic interneurons to oscillatory activity in the CA1 region. In such preparations, with normal extracellular recording solution (containing 2.5 mmol/L K^+; see Discussion for more information), we recorded spontaneously-occurring low-frequency neuronal oscillations in CA1 (0.5–1.5 Hz), in both local field potentials (LFPs) and whole-cell recordings. The slow CA1 oscillations consisted primarily of V_m depolarization, and precise synchronization was found between different CA1 neurons (Fig. 2) (for whole-cell recording, current-clamp mode without applying a holding current was used to measure both V_m and action-potential changes). In addition, the oscillatory V_m

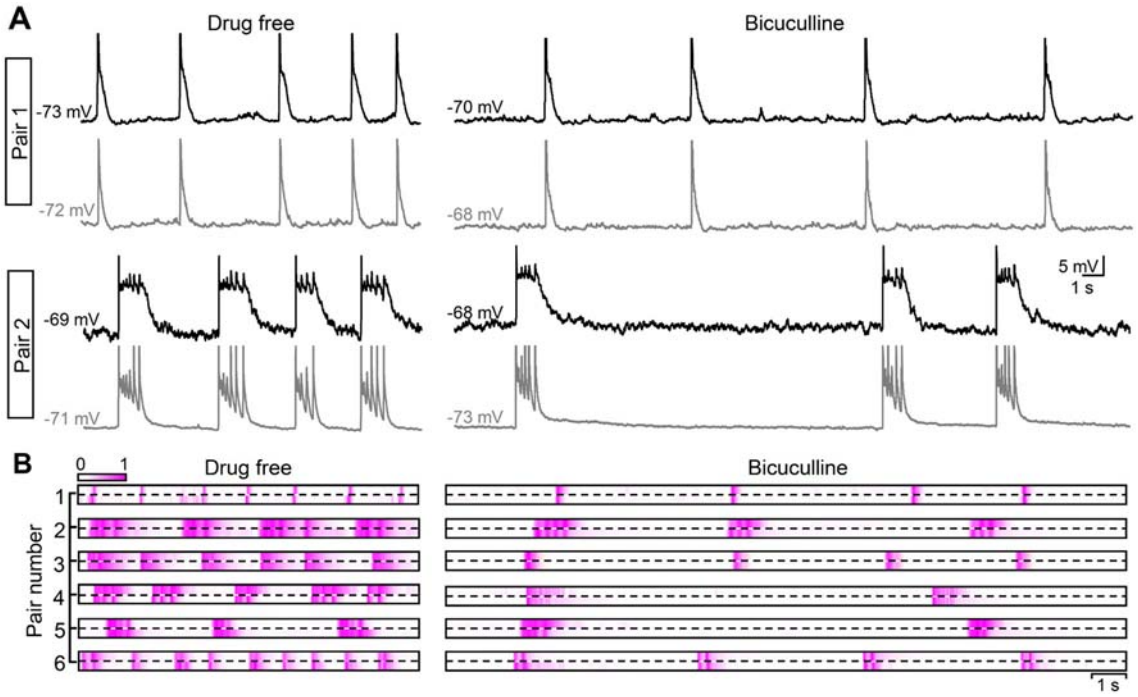

Fig. 4 High correlation of the V_m oscillations remaining under bicuculline. **A** Two paired whole-cell recordings from CA1 neurons displaying highly-synchronized V_m changes that occurred both in the absence and presence of bicuculline. **B** Summary of the synchronized V_m changes recorded in the absence and presence of bicuculline ($n = 6$); data were normalized to the firing threshold for each cell and are indicated by the color scale (with action potentials omitted); data boxed by solid lines are from the two simultaneously-recorded cells (separated by dashed lines).

depolarization was usually suprathreshold for generating single or burst spiking (Fig. 3D).

Oscillations of CA1 PCs are Reduced by Blocking $GABA_A$ Receptors

Next, we investigated the possible role of GABAergic interneuronal networks in generating the CA1 oscillations. By adding the $GABA_A$ receptor antagonist bicuculline (10 μmol/L) to the bath, we found that the CA1 oscillations generated by the complete hippocampus were greatly slowed. As found with whole-cell recording from CA1 PCs ($n = 11$), the frequency of V_m oscillation was reduced from ~0.8 Hz to ~0.2 Hz ($P < 0.001$) and gradually returned to baseline after drug washout (Fig. 3A-C). These results demonstrated that $GABA_A$ receptor-mediated activity increases the frequency of intrinsic CA1 oscillations in excitatory V_m depolarization, although $GABA_A$ receptors primarily mediate inhibitory synaptic responses in the rat hippocampus after the end of the first postnatal week, the age of animals used in this study [27, 28].

Despite the reduction in frequency, the peak amplitude of the oscillation in the presence of bicuculline was not significantly changed and was also usually suprathreshold for generating action potentials (Fig. 3D; $P = 0.26$), and the firing threshold (from resting potential) was unchanged (Fig. 3E; $P = 0.47$). On the other hand, the oscillations remaining in the presence of bicuculline were also highly synchronized between CA1 neurons, similar to those measured under drug-free conditions (Fig. 4). Thus, blocking $GABA_A$ receptor activity causes no significant change in CA1 oscillations with respect to their amplitude and synchronization.

Oscillations of CA1 FS Interneurons are Reduced by Blocking $GABA_A$ Receptors

In the same complete hippocampus *in vitro*, we next determined whether CA1 interneurons also exhibit spontaneous oscillatory activity. In whole-cell recordings from 5 CA1 FS interneurons in the stratum oriens, we found oscillatory V_m depolarization as well as firing in all cells, similar to the recordings from PCs. To test whether the oscillations entrained in FS cells also depended on GABAergic neuronal network activity, we added bicuculline to the bath and found greatly slowed oscillation (from 0.8 Hz to 0.2 Hz; $P = 0.035$; Fig. 5). These data indicate that, similar to CA1 PCs, oscillations in CA1 FS interneurons are generated intrinsically by the hippocampal circuit in a $GABA_A$ receptor-dependent manner.

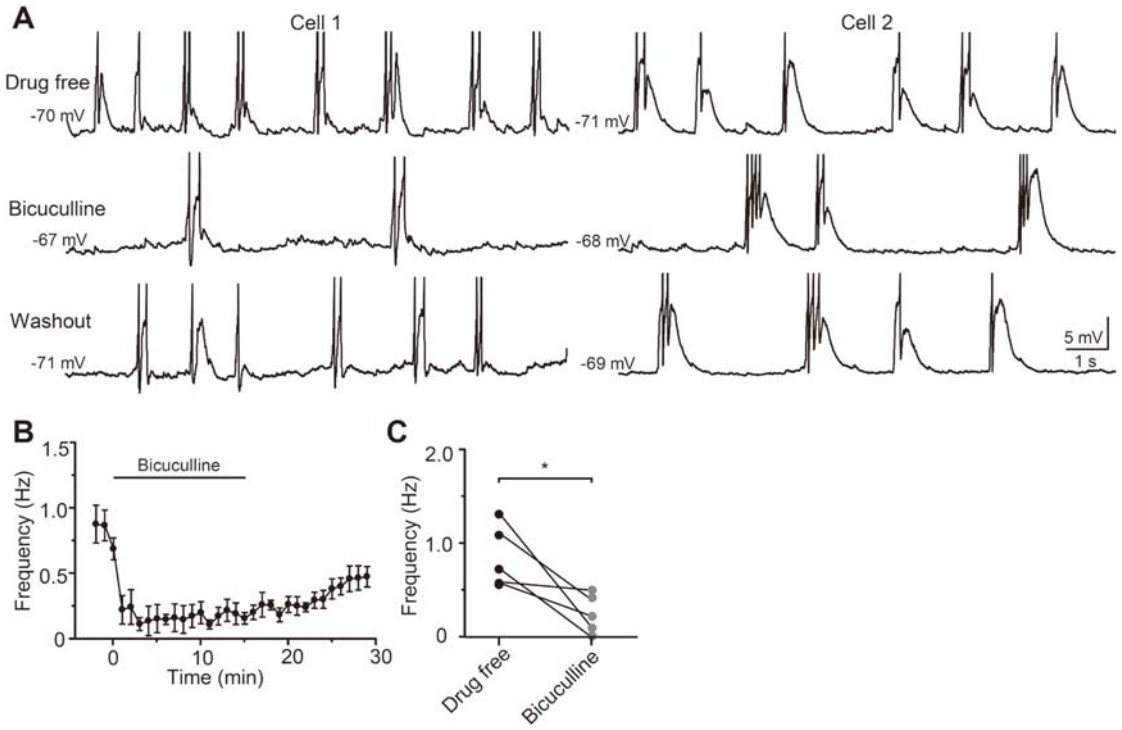

Fig. 5 Bicuculline diminished intrinsically-entrained oscillations in CA1 FS cells. **A** Two examples of CA1 FS cells showing oscillations recorded in the absence and presence of bicuculline. **B, C** For all experiments such as those in A (n = 5), time-course plots for the changes in oscillation frequency averaged across population data (B) and results for all individual neurons (C; data were measured 0–2 min before and 10–15 min after drug application). *P <0.05.

Blocking $GABA_B$ Receptors does not Reduce CA1 Oscillations

We further found that $GABA_B$ receptors, another form of the receptor, exerted little effect on the oscillations in CA1 neurons. In recordings from CA1 PCs, bath application of the $GABA_B$ receptor antagonist SCH50911 (20 or 40 μmol/L) gave rise to little change (P = 0.14) in the frequency of oscillation (Fig. 6).

Enhancement of CA1 Oscillation by Increasing $GABA_A$ Receptor Activity

We further found that increasing $GABA_A$ receptor-mediated activity by adding midazolam (2 μmol/L) to the bath enhanced the CA1 oscillation. As recorded in CA1 PCs (n = 8), the oscillation frequency increased from ~0.6 Hz (before drug application) to ~1.1 Hz (after 10–15 min) after midazolam application (P = 0.027; Fig. 7A–C). Similar to that found with $GABA_A$ receptor blockade (Fig. 3D and E), the peak amplitude of oscillatory V_m depolarization, firing probability (P = 0.30), and threshold (P = 0.16) were not changed by midazolam (Fig. 7D and E).

CA1 FS Cells Generate Action Potentials Before PCs

The above experiments provided evidence that the activity of hippocampal GABAergic interneurons is critical for generating oscillations in the CA1 region. We then performed paired whole-cell recordings from CA1 FS cells in the stratum oriens and CA1 PCs. Our recordings first revealed that V_m oscillations as well as neuronal firing were highly synchronized between CA1 FS cells and PCs (Fig. 8A). We further measured the intervals between action potentials (at the time of the peak; for burst spiking, only the first spike was considered) in FS cells and PCs during single oscillatory cycles. We found that in most recordings (5/8), FS cells always generated preceding action potentials, although in the rest of the recordings, preceding firing alternately emerged in PCs and FS cells (n = 2) or only in PCs (n = 1) (Fig. 8B). The highly-synchronized firing between FS neurons and PCs indicates functional connectivity [29, 30] between these two types of cells, and the significantly larger (P = 0.024) proportion of preceding firing in FS cells further suggests that in such connectivity, FS interneurons may be upstream and PCs downstream.

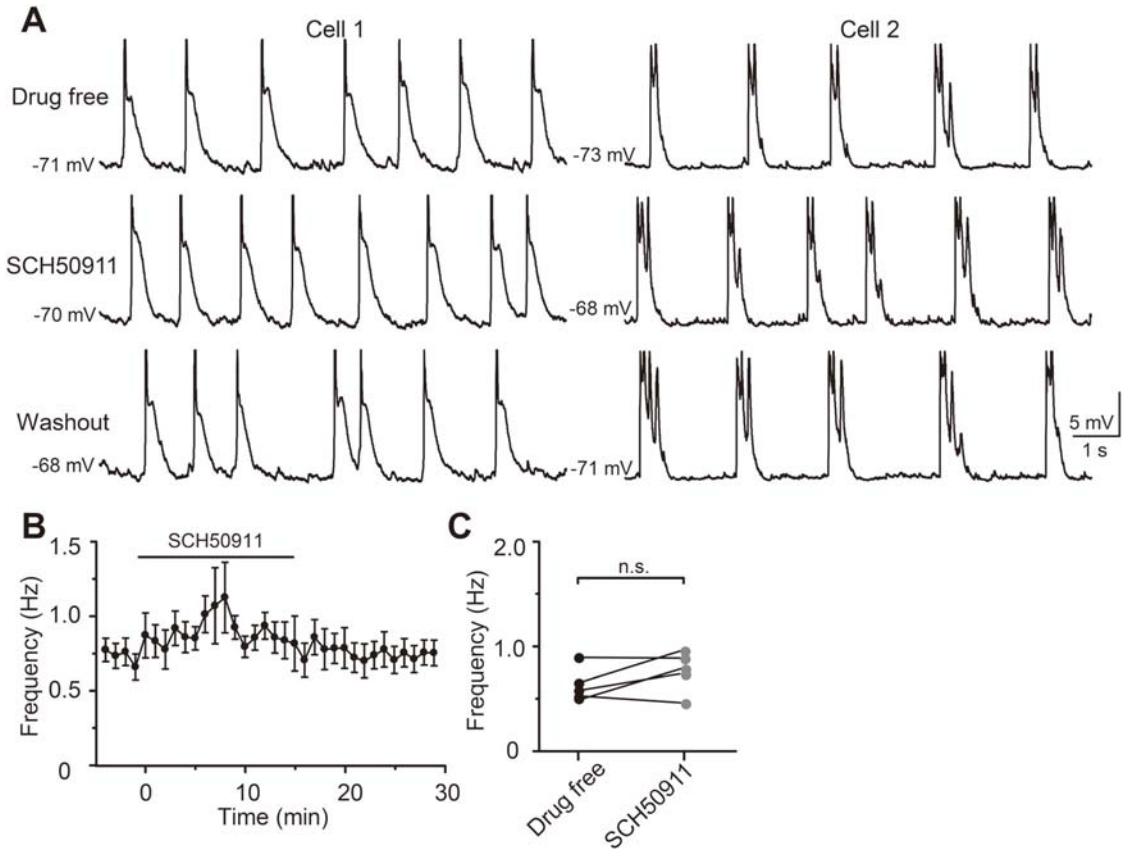

Fig. 6 Blocking $GABA_B$ receptors with SCH50911 did not slow the CA1 oscillations. **A** Two example recordings of oscillations from CA1 PCs measured without and with SCH50911 treatment. **B, C** For experiments such as those in A ($n = 5$), summary of the frequency of V_m oscillations recorded without and with SCH50911 treatment. Data in C were measured 0–4 min before and 10–15 min after drug application.

Effect of Partial Blockade of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid Receptors (AMPARs) on CA1 Oscillations

We next examined the dependence of the CA1 oscillations on the weight of network excitation. For this purpose, we used 0.2, 0.5, and 1 μmol/L DNQX (6,7-dinitroquinoxaline-2,3-dione) to partially block AMPAR-mediated activity. We first found in hippocampal slices that EPSPs elicited in CA1 PCs by Schaffer collateral stimulation underwent a reduction of about 35%, 45%, and 55% by bath application of 0.2, 0.5, and 1 μmol/L DNQX, respectively (Fig. 9A and C).

In the subsequent experiments in the completely isolated hippocampus, we found in PCs that CA1 oscillations were totally blocked by 1 μmol/L DNQX, and in the presence of 0.2 and 0.5 μmol/L DNQX, the oscillations were still generated but at a much lower frequency (Fig. 9B and C). Again (as found in the data shown in Fig. 3D and E), with 0.2 or 0.5 μmol/L DNQX, the peak amplitude of the remaining oscillatory V_m depolarizations, as well as the firing probability and threshold were similar to those recorded under drug-free conditions (Fig. 9D). These findings indicate that under the circumstances in which excitatory synaptic transmission in the network undergoes a certain degree of reduction, the hippocampus produces oscillatory activity at a lower frequency, but each oscillatory event generates excitatory activity of a similar amplitude.

Discussion

In the complete hippocampal formation *in vitro*, we recorded oscillatory V_m depolarizations in both CA1 PCs and FS neurons as well as network synchronization in the CA1 region; these were generated intrinsically at a low frequency (0.5–1.5 Hz). These oscillations relied on GABAergic interneuronal activity, as indicated by the blocking effect of bicuculline on the oscillation entrainment, as well as the large proportion of preceding firing in CA1 FS cells in paired recordings with CA1 PCs. Our findings indicate an effect of GABAergic synaptic transmission on the hippocampal generation of neuronal oscillations by significantly increasing a slow CA1 oscillation.

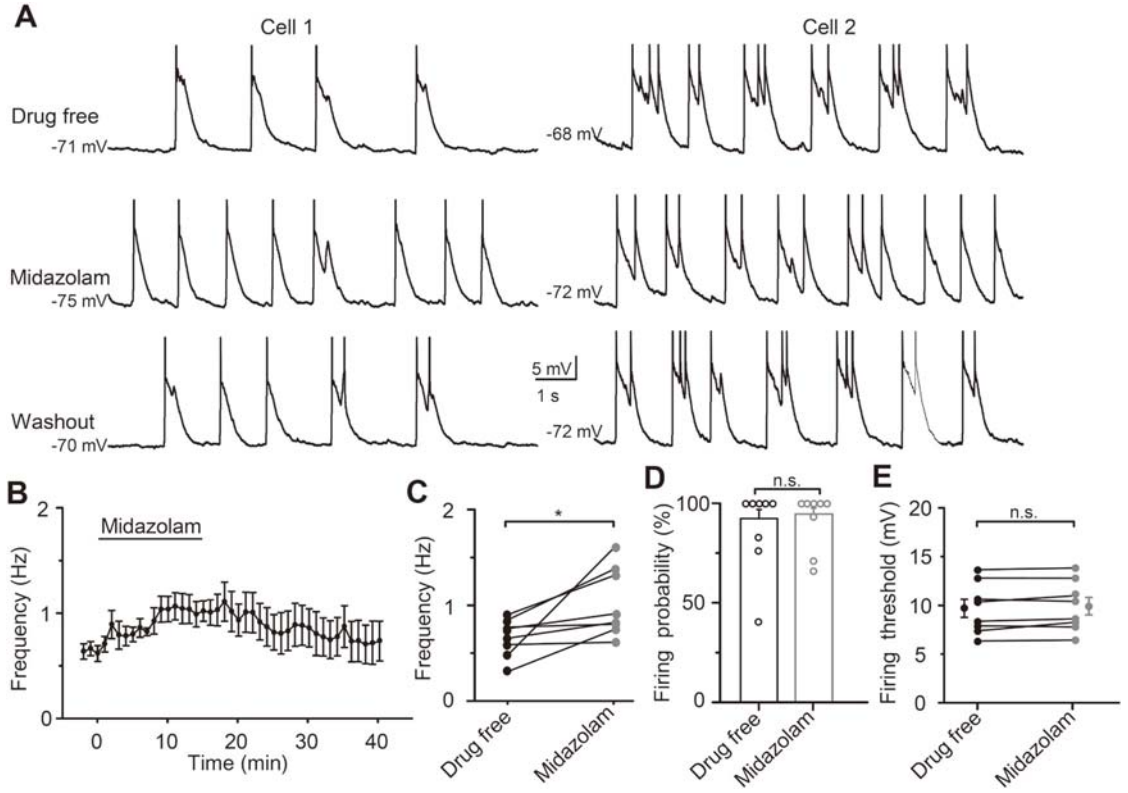

Fig. 7 Midazolam enhanced intrinsically-entrained oscillations in CA1 PCs. **A** Two examples showing V_m oscillations in CA1 PCs recorded in the absence and presence of midazolam. **B** For all experiments such as those in A, time-course plots for the oscillation frequency averaged across population data (n = 8). **C–E** Oscillation frequencies (C), firing probability of oscillatory depolarization (D), and firing thresholds (E; from resting potentials) for all individual cells shown in B. Data were measured 0–2 min before and 10–15 min after drug application. *P <0.05; n.s., not significant.

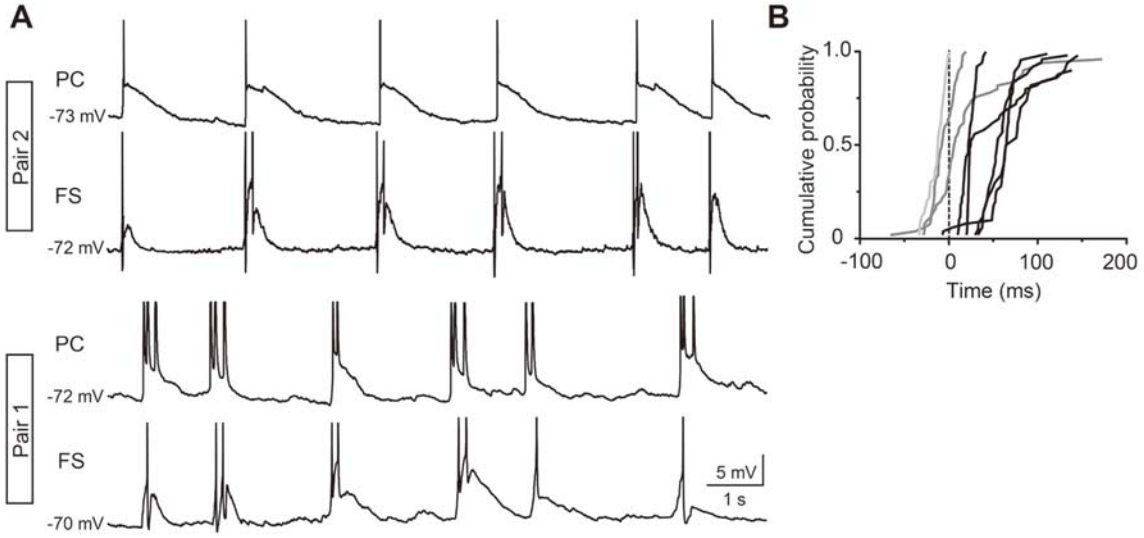

Fig. 8 Preceding firing of CA1 FS cells recorded in paired recordings with CA1 PCs. **A** Two paired recordings showing highly-synchronized V_m changes and discharges. **B** Cumulative distribution plots for the intervals between action potentials (at peak times; for burst spiking, only the first spike was considered) in FS cells and PCs during single oscillatory cycles; firing times of FS cells were subtracted from those of PCs. In 5 out of 8 paired recordings, preceding firing was usually detected in FS cells (black curves); in 2 paired recordings, preceding firing occurred alternately in FS cells and PCs (dark gray curves); and in 1 paired recording, preceding firing was usually detected in PCs (light gray curve).

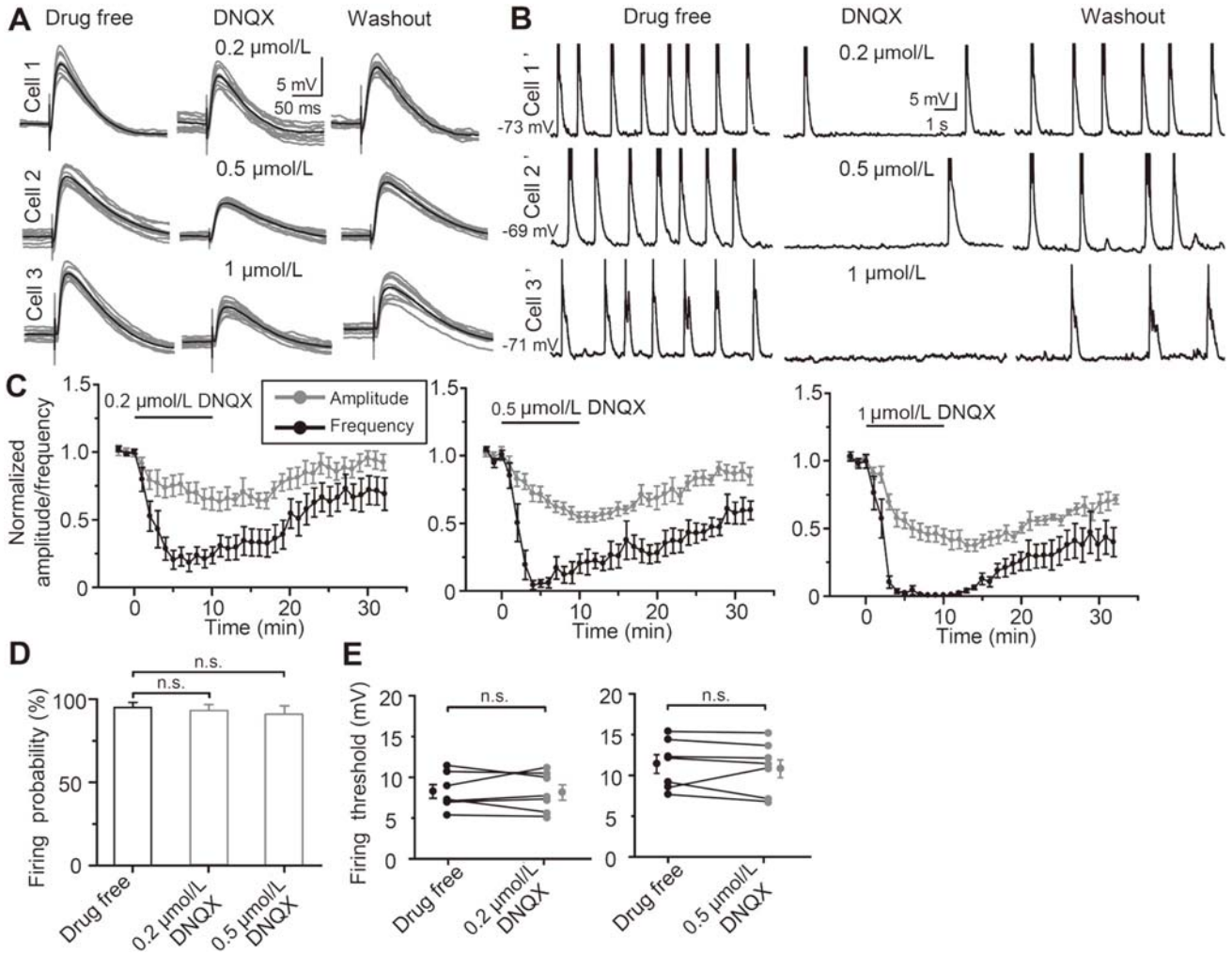

Fig. 9 Effect of partial blockade of AMPARs on CA1 oscillations. **A** Representative recordings from 3 CA1 PCs in brain slices showing 10 consecutive EPSPs elicited by Schaffer collateral stimulation in the absence and presence (5–10 min after drug application) of 0.2, 0.5, and 1 μmol/L DNQX (for washout, the data were taken 20 min after washing). Raw traces are shown in gray and their averages in black. **B** Representative recordings from 3 CA1 PCs in the complete hippocampus showing oscillations recorded in the absence and presence (5–10 min after drug application) of 0.2, 0.5, and 1 μmol/L DNQX (for washout, the data were taken 20 min after washing). **C** Summary of the reduction of EPSPs (for all experiments such as those in A; $n = 7$ for each group of recordings) and oscillation frequencies (experiments such as those in B; $n = 7$ each) caused by 0.2, 0.5, and 1 μmol/L DNQX; data were normalized to the value measured before drug application. **D, E** Firing probability of oscillatory depolarizations (D) and firing thresholds (E) for two of the groups of recordings (0.2 and 0.5 μmol/L DNQX) shown in C. Data were measured 0–2 min before and 5–10 min after DNQX application. n.s., not significant (Student's *t*-test for data shown in D; paired Student's *t*-test for E).

Using a high concentration of K^+ (4–4.5 mmol/L) in the extracellular recording solution, a previous study [25] in a similar complete hippocampus *in vitro* demonstrated a higher frequency of self-generated CA1 oscillations (~5 Hz; theta band), in which inhibitory postsynaptic activity was recorded in CA1 PCs and EPSPs in interneurons. In our preparation of the complete hippocampus, when a high concentration of K^+ was used in the extracellular solution, similar oscillations were seen in CA1, including the high frequency as well as the response properties of PCs and FS cells. With a low K^+ concentration (2.5 mmol/L) in the extracellular solution, we recorded a slower oscillation (0.5–1.5 Hz) that was self-generated in CA1 neurons, and both CA1 PCs and FS cells exhibited EPSP activity. Because our purpose was to investigate the neuronal mechanism accounting for excitatory rhythmic activity generated in the hippocampus, particularly in PCs, we used the low concentration of K^+ in the external solution.

Previous studies have proposed that the interaction between PCs and inhibitory interneurons is critical for generating a network oscillation. As found in brain slices, inhibitory postsynaptic responses elicited by GABAergic

interneurons can give rise to post-inhibitory 'rebound' activation, due to the interaction of inhibitory synaptic events with postsynaptic intrinsic conductances [8]. This process could be involved in the generation of the excitatory V_m oscillations we recorded in CA1 neurons on the basis of loops between hippocampal PCs and interneurons [8, 24], and this possibility was further supported by the finding of preceding firing in FS cells in simultaneous recordings with CA1 PCs.

In addition to the interaction between PCs and interneurons, other mechanisms that rely on GABAergic interneurons could also be used in the hippocampus to generate the CA1 oscillations. One possibility is the existence of a disinhibitory effect on the activity of inhibitory neurons. It is known that GABAergic interneurons innervate not only excitatory neurons, but also make connections with themselves and other inhibitory neurons *via* both chemical and electrical synapses [7, 10, 11]. Blocking $GABA_A$ receptor activity in our experiments may also have greatly reduced the inhibitory synaptic transmission between interneurons, making it possible to reduce CA1 oscillations by changing the excitation-inhibition balance in the network activity. Another possibility is the excitatory nature of some $GABA_A$ receptors. It has been shown that $GABA_A$ receptor-mediated synaptic responses are not always inhibitory, and can be excitatory even in adult animals under normal conditions [31–33]. Blocking such excitatory $GABA_A$ receptors (if they were involved in the oscillation generation in our recordings) could also be responsible for reduction of the CA1 oscillation.

In summary, we recorded a slow CA1 oscillation that was intrinsically generated in the completely isolated hippocampus. This oscillation was composed of excitatory V_m depolarization, and was greatly reduced by blocking $GABA_A$ receptor-mediated activity. Further, we recorded preceding neuronal firing in CA1 FS cells in paired recordings from CA1 PCs. Our findings indicate an effect of GABAergic synaptic transmission on hippocampal oscillations, which significantly increase the frequency of a slow CA1 oscillation.

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