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Somatosensory stimulation suppresses the excitability of pyramidal cells in the hippocampal CA1 region in rats

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Abstract

The hippocampal region of the brain is important for encoding environment inputs and memory formation. However, the underlying mechanisms are unclear. To investigate the behavior of individual neurons in response to somatosensory inputs in the hippocampal CA1 region, we recorded and analyzed changes in local field potentials and the firing rates of individual pyramidal cells and interneurons during tail clamping in urethane-anesthetized rats. We also explored the mechanisms underlying the neuronal responses. Somatosensory stimulation, in the form of tail clamping, changed local field potentials into theta rhythm-dominated waveforms, decreased the spike firing of pyramidal cells, and increased interneuron firing. In addition, somatosensory stimulation attenuated orthodromic-evoked population spikes. These results suggest that somatosensory stimulation suppresses the excitability of pyramidal cells in the hippocampal CA1 region. Increased inhibition by local interneurons might underlie this effect. These findings provide insight into the mechanisms of signal processing in the hippocampus and suggest that sensory stimulation might have therapeutic potential for brain disorders associated with neuronal hyperexcitability.

Key Words: *nerve regeneration; somatosensory stimulation; tail clamping; hippocampal CA1 region; local field potential; unit spike; population spike; excitability; 973 Program; neural regeneration*

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Introduction

The hippocampal region of the brain is known to play important roles in learning and memory formation. Understanding the behavior of individual neurons in the hippocampus is crucial for elucidating the mechanisms of memory formation. Currently, it is not clear how hippocampal neurons respond to inputs from the sensory nervous system (Pereira et al., 2007). Previous investigations have shown that sensory stimulation, such as strokes on the foot or whiskers, evoke different patterns of action potential firing in hippocampal neurons, which can be detected as a change in multiple unit activity (Miller and Groves, 1977; Vinogradova et al., 1993; Pereira et al., 2007). In addition, in response to somatosensory stimulation, the firing of pyramidal cells in the CA1 region decreases, while the firing of interneurons changes intricately—increasing, decreasing or without significant change (Miller and Groves, 1977; Vinogradova et al., 1993; Bellistri et al., 2013). However, the mechanisms responsible for the activity change in pyramidal cells (*i.e.*, the principal cells in the hippocampus) remain unclear. Considering that these cells are modulated by local inhibitory circuits comprised of interneurons (Zheng and Khanna, 2001; Bellistri et al., 2013), the decrease in pyramidal cell firing could be caused by an increase in interneuron-mediated inhibition, or by a decrease in pyramidal cell excitability. In addition, a decrease in afferent input could also affect pyramidal cell activity (Bellistri et al., 2013).

To investigate how pyramidal cells and interneurons respond to somatosensory input in the hippocampal CA1 region, we recorded and analyzed changes in local field potentials and firing rates of individual neurons during tail clamping in urethane-anesthetized rats. We also investigated the mechanisms underlying the neuronal responses.

The urethane anesthetized preparation can avoid the influence of animal's behavior and other unnecessary sensory input (Deadwyler et al., 1981; Itskov et al., 2011) without significant anesthetic effects on somatosensory inputs, because the urethane has minimum inhibition on sensory-evoked responses in nervous systems (Sceniak and Maciver, 2006).

Materials and Methods

Electrode placement and signal recording

A total of 12 clean, healthy, adult, male, Sprague-Dawley rats weighing 250–350 g were provided by the Experimental Animal Center, Zhejiang Academy of Medical Science, China. All procedures used in this study were carried out in accordance with the Guide for the Care and Use of Laboratory Animals (Ministry of Health, China), and the protocol was approved by the Institutional Animal Care Committee of Zhejiang University in China. The rats were intraperitoneal-

ly anesthetized with urethane 1.25–1.50 g/kg, and placed in a stereotaxic apparatus (Stoelting Co., Wood Dale, IL, USA). Part of the skull was removed for placement of electrodes. The recording electrode was a 16-channel microelectrode array (NeuroNexus Technologies, Ann Arbor, MI, USA) that was inserted into the hippocampal CA1 region (anteroposterior, –3.0 mm; mediolateral, 2.6 mm; dorsoventral, 2.5 mm) (George and Charles, 2007) to make extracellular recordings of local field potentials and to record unit spikes. The stimulating electrode was a bundled pair of polyimide insulated tungsten electrodes (A-M Systems Inc., Carlsborg, WA, USA) with a vertical tip separation of about 0.5 mm, and was inserted into the Schaffer collaterals (anteroposterior, −2.0 mm; mediolateral, 2.3 mm; dorsoventral, 2.8 mm) for orthodromic stimulation of CA1 neurons. Two stainless steel screws were fixed in the nasal bone and served as reference and ground. The accuracy of electrode placement was confirmed by the unique waveforms of the orthodromic-evoked potentials in the CA1 region recorded by the electrode array (Kloosterman et al., 2001). Saline was poured over the exposed cortex to maintain moisture.

Stimulus pulses with constant currents were produced by a Model 2300 Stimulus Isolator (A-M Systems Inc.), with a duration of 0.1 ms and a current intensity in the range of 0.25–0.35 mA, that induced orthodromic-evoked population spikes of about 80% maximal amplitude in the CA1 stratum pyramidale. The population spike amplitude was measured as the average of the two potential differences of the negative spike peak to the preceding and following positive peaks.

Signals were first amplified 100-fold by a 16-channel amplifier (Model 3600, A-M Systems Inc.) with a filter frequency range of 0.3–5,000 Hz. Signals were then sampled at 20,000 Hz with a data-acquisition system PowerLab ML880 (AD Instruments Inc., Castle Hill, NSW, Australia) and were stored onto hard disk for offline analysis (Feng et al., 2013).

Signal processing and spike sorting

Using the LabChart software in the PowerLab ML880 suite, the local field potentials were extracted from the raw recording signals by a 0.5–80 Hz digital band-pass filter, then the power spectrum of a 30-second long local field potential signal was estimated using Welch's method (Welch, 1967), *i.e.*, the spectrum was calculated by fast Fourier transformation with a length of 2^{17} sampling data (about 6.55 seconds) in successive 50% overlapping Hanning windows. The frequency resolution of the estimated spectrum was about 0.15 Hz. Then, the power percentages of local field potentials in the following sub-frequency bands were calculated: delta (0.5–2 Hz), theta (2–7 Hz), alpha (7–13 Hz), beta (13–30 Hz) and gamma (30–80 Hz) (Buzsáki and Draguhn, 2004).

The digital high-pass filter provided in the LabChart software with a cut-off frequency of 500 Hz was used to extract the multiple unit activity signals from the raw recordings from the CA1 stratum pyramidale. Unit spikes were then detected using a threshold method (Lewicki, 1998). The threshold values were set as ± 5–8 times the standard deviation of the multiple unit activity signal to minimize error. Signals with amplitudes larger than the threshold were collected as unit waveforms with a duration of 4 ms (2 ms pre-threshold and 2 ms post-threshold). The feature vectors (*i.e.*, principal components) of the unit spike waveforms were extracted with a Matlab program, MClust (http://redishlab.neuroscience.umn.edu/MClust/MClust.html). Then, spike sorting was performed with an open-source automatic clustering software, KlustaKwik (Rutgers University, New Brunswick, NJ, USA) (Harris et al., 2000), which is based on the principal component analysis method.

To distinguish the unit spikes of pyramidal cells from that of interneurons, we calculated the mean waveform widths of the sorted unit spikes. Because the trough to post-peak width for the spike waveforms of a pyramidal cell and an interneuron are 0.86 ± 0.17 ms and 0.43 ± 0.27 ms, respectively (Barthó et al., 2004), a width of 0.7 ms was used to distinguish pyramidal neurons from interneurons. In addition, autocorrelograms of the inter-spike intervals of the sorted unit spikes were used to confirm the judgment of neuronal type. CA1 pyramidal cells usually fire spike bursts of 3–5 or more action potentials with very short inter-spike intervals (Ranck, 1973), yielding two sharp peaks at the short intervals near the center of the autocorrelogram, while autocorrelograms for interneurons appear smooth without sharp peaks (Csicsvari et al., 1999; Barthó et al., 2004).

The raster plots and the peristimulus time histogram of sorted unit spikes were used to calculate the change in firing rate of single neurons 30 seconds before and 30 seconds after the onset of somatosensory stimulation (tail clamping). In the peristimulus time histogram, the bin width of the horizontal axis was set at 1 second. Plots of peristimulus time histogram were also used to show the change in firing rate of multiple unit spikes.

Somatosensory stimulation

Somatosensory stimulation was applied by clamping the tail for 3 minutes using a crocodile clip with a length of 35 mm (Sute Inc., Shanghai, China) (Bermudez Contreras et al., 2013).

Statistical analysis

All data were expressed as mean ± SD, and analyzed using SPSS for Windows (SPSS, Chicago, IL, USA). Paired *t*-test was used to evaluate differences in firing rates of pyramidal cells and interneurons before and during somatosensory stimulation. One-way analysis of variance and repeated analysis of variance with *post hoc* Bonferroni tests were used to compare differences in the power spectra of local field potentials and the amplitudes of orthodromic-evoked population spikes before, during and after somatosensory stimulation.

Results

Changes in local field potentials and multiple unit activity under somatosensory stimulation

The local field potential signal in the stratum pyramidale of the CA1 region was examined from one channel of the recording electrode array (**Figure 1A**). The waveforms of local

field potentials changed immediately following the onset of tail clamping with a clip and were maintained for 3 minutes until the removal of the clip. Before tail stimulation, the local field potentials exhibited large-amplitude slow activity with a main power in the delta band. However, during the tail clamping period, local field potentials changed into a theta rhythm-dominated waveform. After removing the clip, the local field potentials recovered quickly to the original slow rhythm (**Figure 1B**).

The changes in local field potentials were quantified using power spectrums for 30-second episodes of local field potential signals before and following the onset of tail clamping, as well as after the end of tail clamping. As shown in **Figure 1C,** during tail clamping, the power percentage of the delta rhythm significantly decreased by 54.5 ± 13.2% (one-way analysis of variance, $F > 283.8$, $P < 0.001$; with *post hoc* Bonferroni test, $P < 0.001$; $n = 12$), while that of the theta rhythm significantly increased by 25.5 ± 9.0% (one-way analysis of variance, $F > 24.7$, $P < 0.001$; with *post hoc* Bonferroni test, $P < 0.001$; $n = 12$). The power percentages of the other three bands with higher frequencies were also increased significantly during tail clamping, but their powers were far less than the theta band.

The significant changes in local field potential induced by somatosensory stimulation might be associated with changes in unit spike activity. Therefore, the peristimulus time histogram plots of multiple unit activity were used to show the differences in firing rates of the multiple unit spikes in the period 30 seconds before and 30 seconds following the onset of tail clamping. However, there were no consistent multiple unit activity changes ($n = 12$). Some of the peristimulus time histogram plots showed a decrease in spike firing rate following the onset of tail clamping (**Figure 1D**), while others did not show obvious changes (**Figure 1E**). Our investigation of single unit activity suggested that the inconsistent changes in multiple unit activity could be caused by the activity of different types of neurons, not by variations in tail clamping or other factors.

Studies have shown that an increase in theta rhythm in the local field potential in the hippocampal CA1 region is usually accompanied by an increase in firing of interneurons (Buzsáki et al., 1986; Toth et al., 1993; Buzsáki, 2002; Bienvenu et al., 2012). In addition, it has been shown that somatosensory stimulation decreases the firing of pyramidal cells in the CA1 region (Bellistri et al., 2013). Therefore, we next examined whether tail clamping could induce contrasting changes in pyramidal cells and interneurons in the CA1 region, which could account for the inconsistent changes in multiple unit activity.

Different responses of pyramidal cells and interneurons induced by somatosensory stimulation

To study the responses of pyramidal cells and interneurons to somatosensory stimulation, we sorted the multiple unit activity signals into single unit spikes, and then distinguished the two types of neurons based on the widths of spike waveforms and the autocorrelogram of inter-spike-intervals. As shown in **Figure 2A**, the superimposed spike waveforms of the pyramidal neurons have a longer trough to post-peak interval than the spike waveforms of interneurons. The autocorrelogram of pyramidal neurons usually contains obvious peaks at very short inter-spike intervals, while that of interneurons does not have this feature. In this study, 10 pyramidal cells and 17 interneurons with an original firing rate greater than 2 spikes/s were obtained from 12 rats. The raster plots of these neurons showed that under tail clamping, the spike firing rates of pyramidal cells decreased, while that of interneurons increased (**Figure 2B**). The average peristimulus time histogram plots of the two types of neurons also clearly showed these opposite changes induced by somatosensory stimulation (**Figure 2C**). The firing rates of the neurons in the two 30-second periods before and after the onset of tail clamping were calculated. The firing rates of pyramidal cells decreased significantly from 3.0 ± 1.6 to 1.1 ± 0.9 spike/s (paired *t*-test, $P < 0.001$, $n = 10$), and that of interneurons increased significantly from 3.3 ± 1.3 to 7.1 ± 7.7 spike/s (paired *t*-test, $P < 0.05$, $n = 17$; **Figure 3**). Opposite changes in firing in different types of neurons might explain the inconsistent multiple unit activity responses that reflected mixed unit spikes of pyramidal cells and interneurons.

These data indicate that somatosensory stimulation can enhance the activation of interneurons in the CA1 region. Considering that interneurons have inhibitory effects on primary neurons, the decrease in firing of pyramidal cells induced by somatosensory stimulation could be caused by a decrease in excitability of pyramidal cells or by a decrease in excitatory input from Schaffer collaterals (Miller and Groves, 1977; Herreras et al., 1986). Therefore, we examined changes in the excitability of pyramidal cells under somatosensory stimulation by applying stimulation pulses on the afferent Schaffer collateral pathway with a constant current intensity.

Somatosensory stimulation suppressed the excitability of pyramidal cells in the CA1 region

To investigate the changes in the excitability of pyramidal cells, electrical pulses with a constant current of 0.25–0.35 mA were applied on the Schaffer collaterals in the CA1 region. The test stimulus was applied before and after the onset of tail clamping, as well as after the release of tail clamping. As shown in **Figure 4**, the stimulus evoked orthodromic population spikes with a large amplitude (7.2 ± 1.8 mV) in the CA1 pyramidal layer before the onset of the tail clamping. In comparison, during tail clamping, the same stimulus evoked population spikes with a significantly reduced amplitude (5.1 ± 2.5 mV). After the release of tail clamping, the population spike amplitudes returned to the original level (6.8 ± 1.8 mV, $n = 12$). This result shows that constant afferent inputs induce smaller responses in CA1 pyramidal cells during tail clamping, indicating that somatosensory stimulation can suppress pyramidal cell excitability.

Discussion

This study shows that somatosensory stimulation changes local field potentials into theta rhythm waveforms and decreases the spike firing of pyramidal cells, while increasing

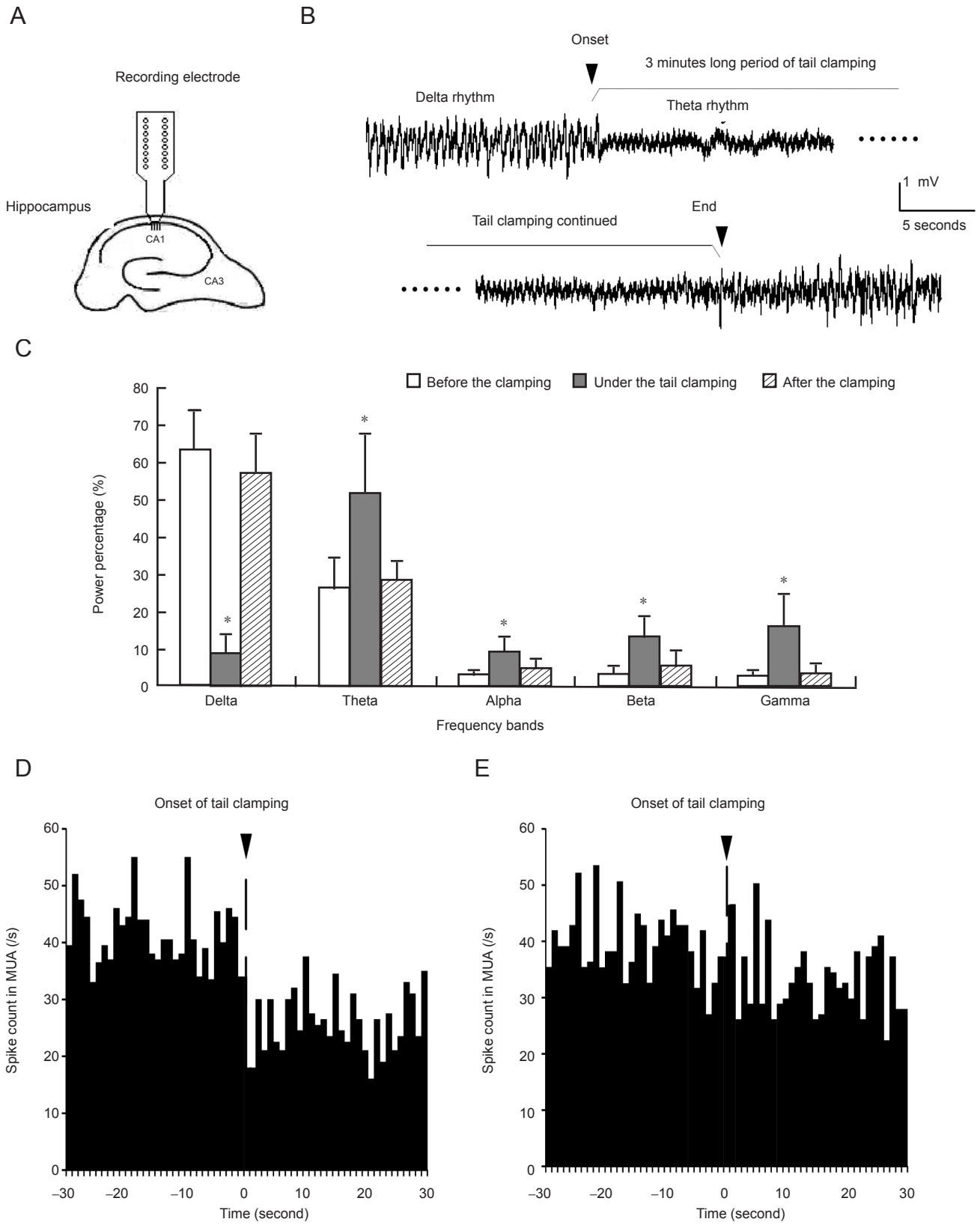

Figure 1 Changes in local field potentials and multiple unit activity (MUA) under somatosensory stimulation.
(A) A microelectrode array was used to record local field potentials and MUA in the hippocampal CA1 region. (B) Local field potentials turned into a theta rhythm dominated waveform under tail clamping and recovered quickly to the original delta rhythm-dominated waveform after removing the clip. (C) The changes in the power spectra of local field potentials 30 seconds before and 30 seconds following the onset of tail clamping, as well as 30 seconds after the end of tail clamping. Data are expressed as mean ± SD. One-way analysis of variance with *post hoc* Bonferroni tests was used to evaluate differences in local field potential power spectra before, during and after somatosensory stimulation. $*P < 0.05$, *vs.* before tail clamping. (D, E) Two examples of the peristimulus time histogram plots of MUA in the time interval of −30 seconds to +30 seconds, with tail clamping started at 0 second.

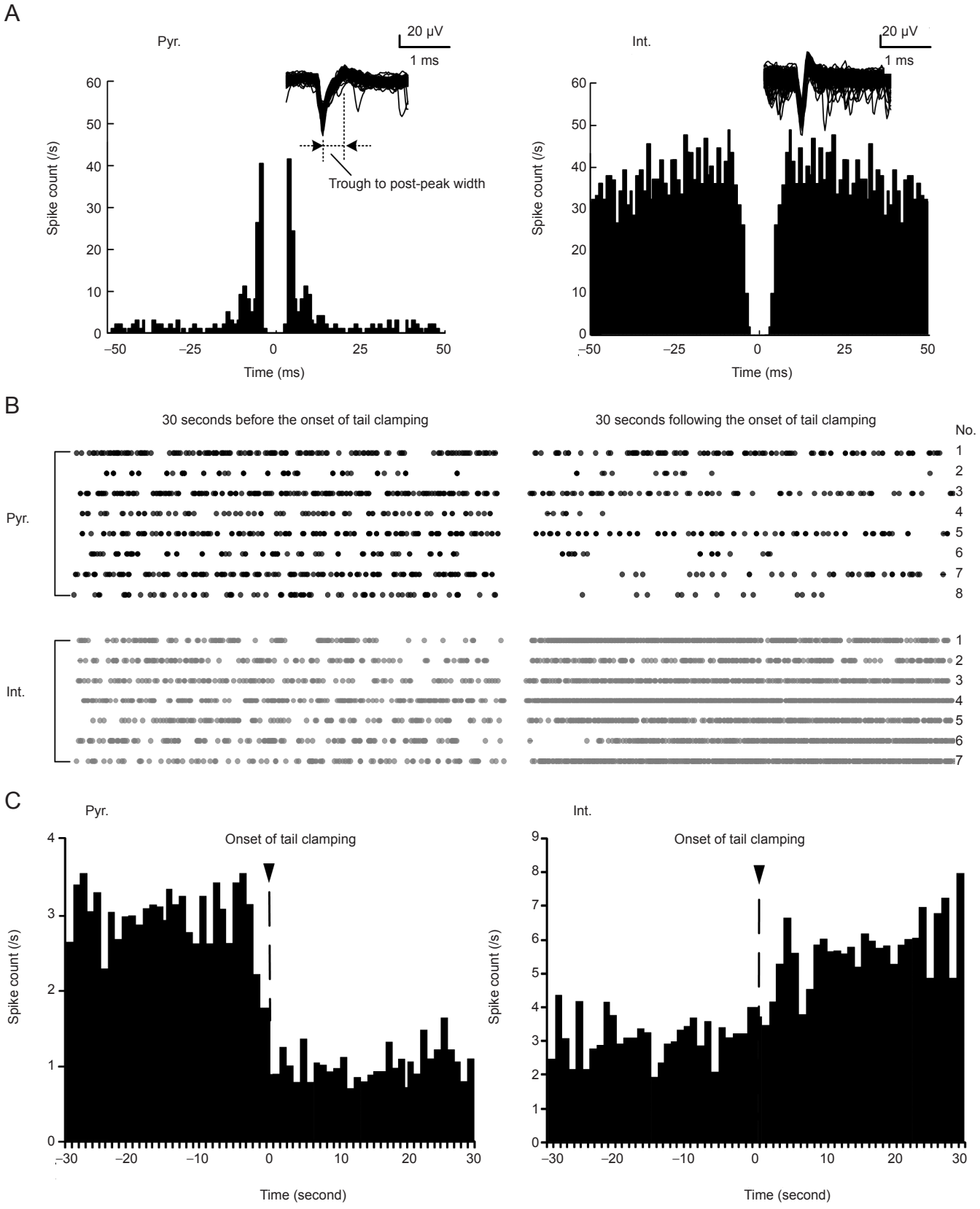

Figure 2 Different responses of pyramidal cells and interneurons induced by somatosensory stimulation.
(A) The differences in the width of spike waveforms and the autocorrelogram of inter-spike intervals between pyramidal cells and interneurons. (B) Raster plots of the neurons showed that under somatosensory stimulation (tail clamping), the spike firing rates of pyramidal cells (Pyr.) decreased, but that of interneurons (Int.) increased instead. (C) Average peristimulus time histogram of the pyramidal neurons and interneurons exhibited in (B).

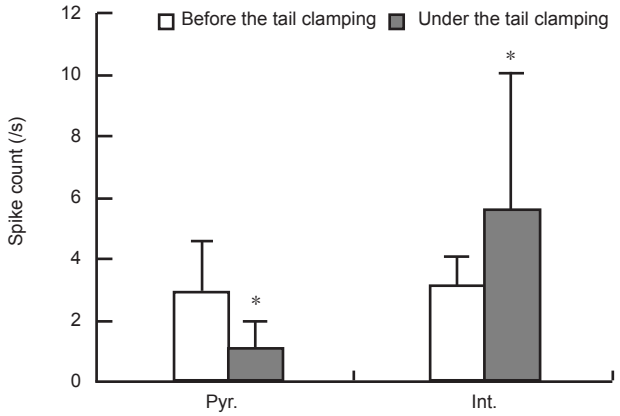

Figure 3 Comparison of the firing rates of pyramidal cells (Pyr.) and interneurons (Int.) between the two 30-second periods obtained before and after the onset of tail clamping.
Data are represented as mean ± SD. There were 10 Pyr. and 17 Int. Paired *t*-test was used to estimate the significant differences in the firing rates of pyramidal cells and interneurons before and during somatosensory stimulation. $*P < 0.05$, *vs.* before tail clamping.

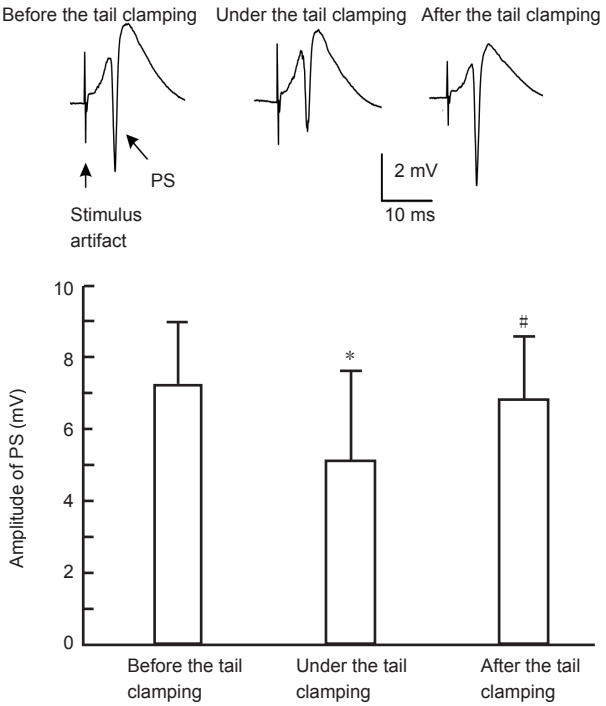

Figure 4 Somatosensory stimulation significantly decreases the amplitude of orthodromic-evoked population spikes (PSs) in the CA1 region.
The three waveforms on the top show typical PSs obtained before, during and after tail clamping. Data are expressed as mean ± SD. Repeated analysis of variance with *post hoc* Bonferroni tests was used to evaluate differences in the amplitudes of orthodromic-evoked PSs before, during and after somatosensory stimulation. $*P < 0.05$, *vs.* before tail clamping; $\#P < 0.05$, *vs.* under tail clamping.

the firing of interneurons. In addition, the attenuation of orthodromic-evoked population spikes indicates a decrease in the excitability of CA1 pyramidal cells by somatosensory stimulation.

Somatosensory input pathways in the brain project to the primary somatosensory cortex, then pass through the entorhinal cortex to enter the hippocampus (Zainos et al., 1997; Melzer et al., 2006). The inputs from the entorhinal cortex to the hippocampal CA1 region can either directly or indirectly (through CA3 and Schaffer collaterals) excite the dendrites of pyramidal cells in the CA1 (Lee et al., 2004; Andersen et al., 2006; Cutsuridis et al., 2010). However, during somatosensory stimulation, the firing of pyramidal cells in the CA1 decreases, instead of increasing, consistent with other studies (Khanna, 1997; Zheng and Khanna, 2001; Bellistri et al., 2013). Local network properties in the CA1 region can explain this phenomenon.

In the CA1, the excitability of pyramidal cells is modulated by local inhibitory circuits consisting of interneurons (Alger and Nicoll, 1982; Papatheodoropoulos and Kostopoulos, 1998; Margineanu and Wülfert, 2000). Somatosensory inputs from both the entorhinal cortex and Schaffer collaterals can excite these interneurons (Lee et al., 2004; Andersen et al., 2006; Cutsuridis et al., 2010). This point is corroborated by the appearance of a strong theta rhythm in the local field potential during somatosensory stimulation, because the firing of interneurons can generate theta rhythms in the CA1 (Alonso and Köhler, 1982; Buzsáki et al., 1986; Toth et al., 1993; Buzsáki, 2002). Presumably, the significantly enhanced activity of interneurons suppresses the excitability of pyramidal cells through local inhibitory circuits, resulting in reduced pyramidal cell activity. In addition, the suppression of orthodromic-evoked population spikes during somatosensory stimulation suggests that pyramidal cell excitability was reduced. Therefore, the present findings suggest that sensory information can decrease rather than increase the activity of pyramidal neurons in the hippocampus.

The present study suggests that the somatosensory-induced suppression of neuronal excitability under anesthesia may have therapeutic potential for abnormal brain states involving neuronal hyperactivity, such as epilepsy during sleep. Non-rapid eye movement sleep has been shown to facilitate the occurrence of seizures and epileptiform abnormalities (Matos et al., 2010; van Golde et al., 2011). In addition, small-wave desynchronized activity during arousal and rapid eye movement stages can reduce epileptiform activity (Matos et al., 2010). Our experiments were carried out under anesthesia. Large-amplitude slow waves in the delta frequency range (< 2 Hz) dominated the local field potentials during anesthesia, indicating a state that was similar to non-rapid eye movement sleep. The increase in inhibitory interneuron activity during tail clamping characterized by theta-dominated small amplitude local field potentials provides insight into the mechanisms underlying epilepsy suppression. Moreover, a previous study showed that somatosensory stimulation, such as fur stroking, abolishes interictal spike activity in epileptic animals (Lerma et al., 1984). Therefore, somatosensory stimulation may be a potential therapeutic approach for some types of neuronal hyperactivity. However, more investigations with epileptic animals are necessary to evaluate the impact of sensory stimulation on seizure activity.

Although tail clamping may represent a noxious pain stimulus, the alterations in the firing of pyramidal cells induced by

tail clamping are consistent with previous studies of moderate stimulation such as strokes on paws and whiskers (Miller and Groves, 1977; Vinogradova et al., 1993; Bellistri et al., 2013). Therefore, our results support the notion that different sensory inputs induce similar responses in the hippocampal region because they share common pathways of information processing (Bellistri et al., 2013). By using tail clamping, we can obtain consistent individual neuronal responses, which can facilitate statistical analysis of activity changes in individual neurons in a moderately long period. Therefore, tail clamping appears to be a simple and reliable method for investigating the mechanisms of somatosensory stimulation.

In conclusion, somatosensory stimulation suppresses pyramidal cell excitability and firing in the hippocampal CA1 region. Increased inhibition by local interneurons might underlie this effect of the sensory input. Taken together, our findings provide valuable insight into the mechanisms of signal processing in the hippocampus. They also suggest that somatosensory stimulation may have therapeutic potential in brain disorders characterized by neuronal hyperactivity (Lerma et al., 1984).

Author contributions: *Wang Y and Feng ZY wrote this manuscript. All authors designed, performed and evaluated the study, and approved the final version of the paper.*
Conflicts of interest: *None declared.*

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