

## RAPID COMMUNICATION

## Switching Between “On” and “Off” States of Persistent Activity in Lateral Entorhinal Layer III Neurons

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**ABSTRACT:** Persistent neural spiking maintains information during a working memory task when a stimulus is no longer present. During retention, this activity needs to be stable to distractors. More importantly, when retention is no longer relevant, cessation of the activity is necessary to enable processing and retention of subsequent information. Here, by means of intracellular recording with sharp microelectrode in *in vitro* rat brain slices, we demonstrate that single principal layer III neurons of the lateral entorhinal cortex (EC) generate persistent spiking activity with a novel ability to reliably toggle between spiking activity and a silent state. Our data indicates that in the presence of muscarinic receptor activation, persistent activity following an excitatory input may be induced and that a subsequent excitatory input can terminate this activity and cause the neuron to return to a silent state. Moreover, application of inhibitory hyperpolarizing stimuli is neither able to decrease the frequency of the persistent activity nor terminate it. The persistent activity can also be initiated and terminated by synchronized synaptic stimuli of layer II/III of the perirhinal cortex. The neuronal ability to switch “On” and “Off” persistent activity may facilitate the concurrent representation of temporally segregated information arriving in the EC and being directed toward the hippocampus. © 2007 Wiley-Liss, Inc.

**KEY WORDS:** hippocampal formation; intrinsic properties; cholinergic modulation; post-stimulus spiking; persistent spiking activity

## INTRODUCTION

Persistent activity occurs in different regions of the central nervous system (Andrade, 1991; Fraser and MacVicar, 1996; Klink and Alonso, 1997; Egorov et al., 2002; Shu et al., 2003; Loewenstein et al., 2005), and such activity in the cortex presumably enables neurons to encode

and maintain information for short-term memory (e.g. working memory) (Goldman-Rakic, 1995; Miller and Cohen, 2001). While several studies have focused on how this activity may persist in the presence of distractors (Egorov et al., 2002; Koulakov et al., 2002; Fransén et al., 2006), cessation of this robust firing has received little attention (Fransén et al., 2002, Soc. Neurosci., abstract). For instance, in a discrete trial delayed match to sample task of object recognition, animals are presented with a sample stimulus during the sample period, and then the animal must ignore different non-match distractor stimuli during a delay period, and finally it must respond if a match stimulus is presented again (Suzuki et al., 1997). Importantly, after the second matching presentation, the sample stimulus must be forgotten in order not to interfere with subsequent inputs. Thus, robust delay activity must be generated and terminated reliably following sensory inputs.

The lateral entorhinal cortex (LEC) is a crucial component of the medial temporal lobe memory system, based on its neuronal connections (Witter et al., 1989) and neural activity (Higuchi and Miyashita, 1996; Suzuki et al., 1997; Young et al., 1997). Neuro-anatomical tracing studies showed that superficial cell layers of the LEC are one of the targets of association cortices (Burwell and Amaral, 1998a), and that the LEC mainly receives non-spatial information (e.g., information necessary for object recognition) (Knierim et al., 2006). Moreover, principal neurons of layers II and III of LEC are one of the main inputs to the hippocampus (Steward, 1976). In this respect, layer III of the LEC provides direct associational inputs to region CA1, which is a primary focus of research on memory related neural activity and cellular mechanisms of memory. Neurophysiological studies demonstrate that LEC neurons are able to generate persistent activity during the delay period of different working memory tasks (Suzuki et al., 1997; Young et al., 1997). Moreover, *in vivo* investigations indicate that the maintenance and encoding of memories is associated with elevation of acetylcholine (ACh) concentration (Tang and Aigner, 1996), and pharmacological studies confirm that muscarinic receptor blockade reduces persistent activity, and impairs the formation of long-term memory (Schon et al., 2005; Hasselmo and Stern,

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2006). Since cholinergic activation is crucial for a correct performance of a memory task, and layer III LEC principal neurons are also important in gating the flow of information to the hippocampus, we decided to investigate whether muscarinic receptor activation induces a mnemonic signature in these neurons.

## MATERIALS AND METHODS

All experimental procedures were approved by the McGill University Animal Care Committee and were in compliance with the guidelines of the Canadian Council on Animal Care. Conventional sharp micro-electrode intracellular recordings were performed on brain slices obtained from male adult Long-Evans rats (150–250 g, Charles River Canada, Saint-Constant, QC, Canada). Semicoronal *in vitro* slices (450  $\mu\text{m}$  thick) were prepared following the protocol explained previously (de Villers-Sidani et al., 2004; Tahvildari and Alonso, 2005). All drugs and chemicals were purchased from Sigma Chemical (Oakville, ON, Canada). Normal Ringer solution was prepared for daily requirements and contained (in mM): 124 NaCl, 3 KCl, 1.6  $\text{CaCl}_2$ , 1.8  $\text{MgSO}_4$ , 26  $\text{NaHCO}_3$ , 1.25  $\text{NaH}_2\text{PO}_4$ , and 10 glucose [pH was adjusted at 7.4 by continuous application of  $\text{O}_2/\text{CO}_2$  (95/5%)].

Recordings were performed in an interface recording chamber (Fine Science Tools, North Vancouver, BC, Canada) at  $34 \pm 1^\circ\text{C}$ . Borosilicate glass electrodes (World Precision Instruments, Sarasota, FL) were pulled on a Brown Flaming puller (Model P-97, Sutter Instruments, Novato, CA), and backfilled with 2 M  $\text{K}^+$ -acetate and 2% biocytin (tip resistance of 80–120  $\text{M}\Omega$ ). Electrical signals were amplified using an Axoclamp 2B amplifier (Axon Instruments, Union City, CA), low-pass filtered at 5 kHz, digitized at 10 kHz by Digidata 1320 (Axon Instruments) and stored on a Pentium computer using Axoscope software (Axon Instruments) for subsequent and further analysis. Cortical layers were identified during experiments by the help of a dissecting microscope (World Precision Instruments). However, locations of recordings were also verified later with biocytin staining according to the protocol explained previously (Tahvildari and Alonso, 2005). Since the muscarinic phenomenon studied did not desensitize, most of the neurons were directly impaled in the presence of carbachol (CCh) ( $n = 40$  out of 60). Electrophysiological data were analyzed using Clampfit 9.0 (Axon Instruments), Origin 6.0 (Microcal Software, North Hampton, MA) software packages. Average values were expressed as means  $\pm$  SE. Statistical significance was evaluated by means of the two-tail Student's *t*-test for paired data.

## RESULTS

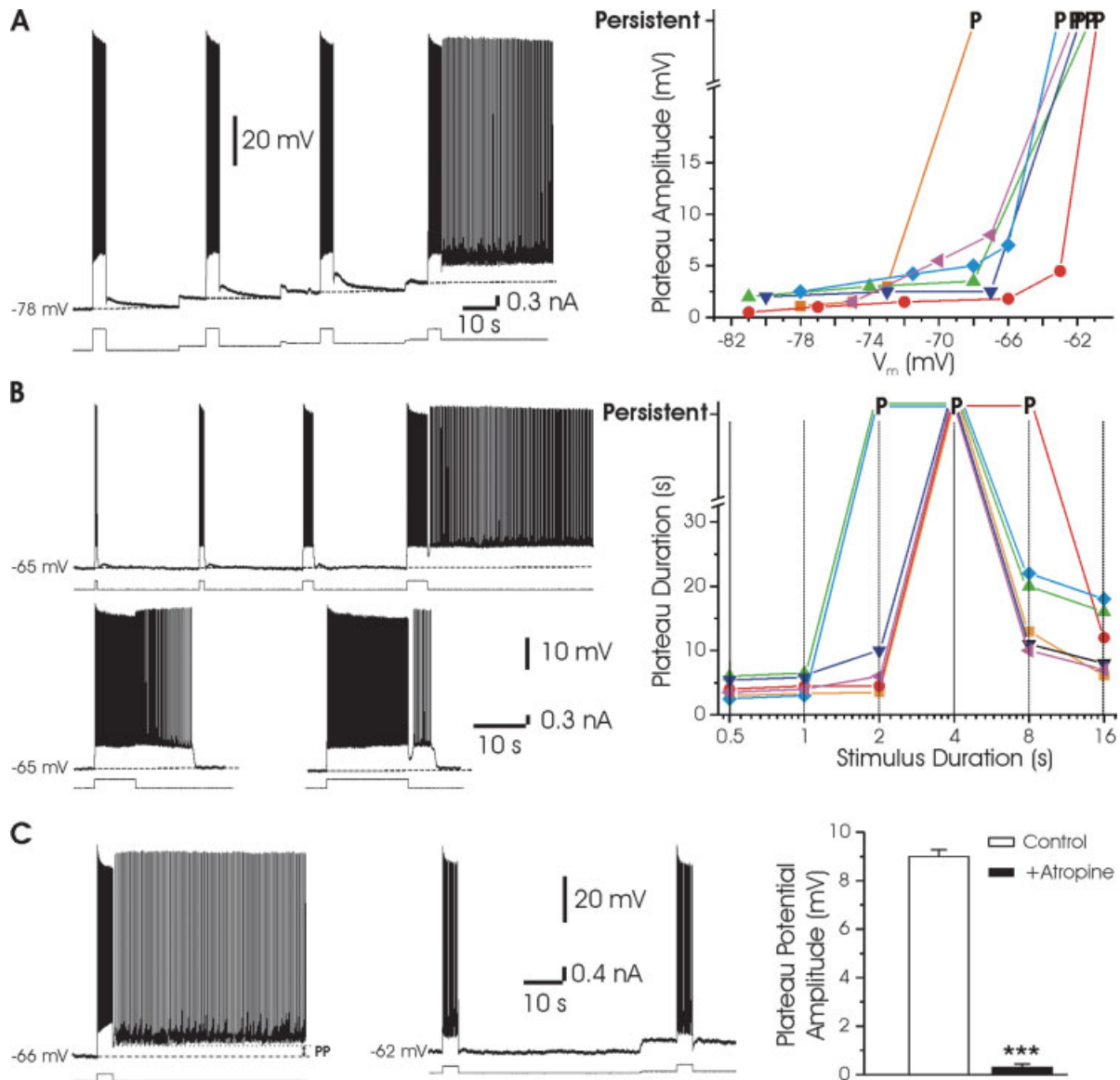
In this study, 60 principal neurons of layer III of the LEC were recorded and labeled intracellularly with the sharp micro-electrode technique. All recorded neurons were identified as pyramidal in shape and they had regular firing patterns as previ-

ously reported (Tahvildari and Alonso, 2005). To investigate the effect of cholinergic modulation solely on the neuronal intrinsic properties and to avoid synaptic interference, the majority of recordings ( $n = 50$ ) were performed during glutamatergic and GABA-mediated neurotransmitter block with kynurenic acid (2 mM) and picrotoxin (100  $\mu\text{M}$ ), respectively.

We observed that bath application of CCh (10  $\mu\text{M}$ ), a non-hydrolyzable cholinergic agonist, changed neither the resting membrane potential (RMP) of layer III LEC neurons (RMP =  $-72.14 \pm 0.43$  and  $-71.88 \pm 0.39$  mV before and after application of CCh, respectively;  $n = 20$ ;  $P > 0.4$ ) nor their input resistance (IR) (IR =  $56.11 \pm 2.26$  and  $56.85 \pm 2.33$   $\text{M}\Omega$  before and after application of CCh, respectively;  $n = 20$ ;  $P > 0.1$ ). It was reported previously that these neurons generate adapting regular firing discharges during application of a suprathreshold depolarizing current pulse which is followed by slow hyperpolarizing after-potentials (Tahvildari and Alonso, 2005). In this study, we observed that bath application of CCh suppressed the slow hyperpolarizing after-potentials appearing after a depolarizing current injection.

We found that depolarizing current injection pulses in the presence of CCh were able to trigger the development of a plateau potential that could be accompanied by post-stimulus spikes if the suprathreshold pulses were triggered from a holding membrane potential more depolarized than  $-70$  mV (Fig. 1A). Moreover, it was observed that from more depolarized levels (between about  $-65$  and  $-60$  mV) these post-stimulus spikes can generate persistent spiking activity with a stable frequency which might last for several minutes (range 8–12 min;  $n = 5$ ). In the following analysis, we always considered activity as persistent when we observed sustained spiking activity at a stable frequency for a duration of 40–60 s.

In the next step, we investigated the relation between the duration of the plateau potential (or post-stimulus spikes) and that of the injected current pulse. We chose injection duration as the changeable parameter, which allowed us to apply step depolarizing current pulses with a broad range of duration values. We observed that from holding membrane potentials around  $-65$  mV in all tested neurons ( $n = 6$ ), application of short pulses (0.5–1 s) was not sufficient to trigger a plateau potential which could generate accompanying post-stimulus spikes. In addition, application of prolonged current pulses above 8 s induced self-terminating post-stimulus spikes (Fig. 1B). However, a 4-s suprathreshold current pulse that triggered firing frequency at 20–30 Hz was always sufficient to induce persistent activity in all tested neurons (Fig. 1B). Shorter or longer duration pulses were generally not able to induce persistent activity, but in some cases either 2-s (2 out of 6) or 8-s (1 out of 6) pulses were also able to trigger persistent activity (Fig. 1B). Thus, in further experiments presented here, we always used 4-s pulses for inducing persistent spiking. Finally, we were able to completely block the activity-dependent plateau potential and associated persistent activity by bath application of the muscarinic antagonist atropine (1  $\mu\text{M}$ ; Fig. 1C;  $n = 4$ ) suggesting that muscarinic receptors are mediating the generation of the persistent spiking activity in the presence of carbachol.

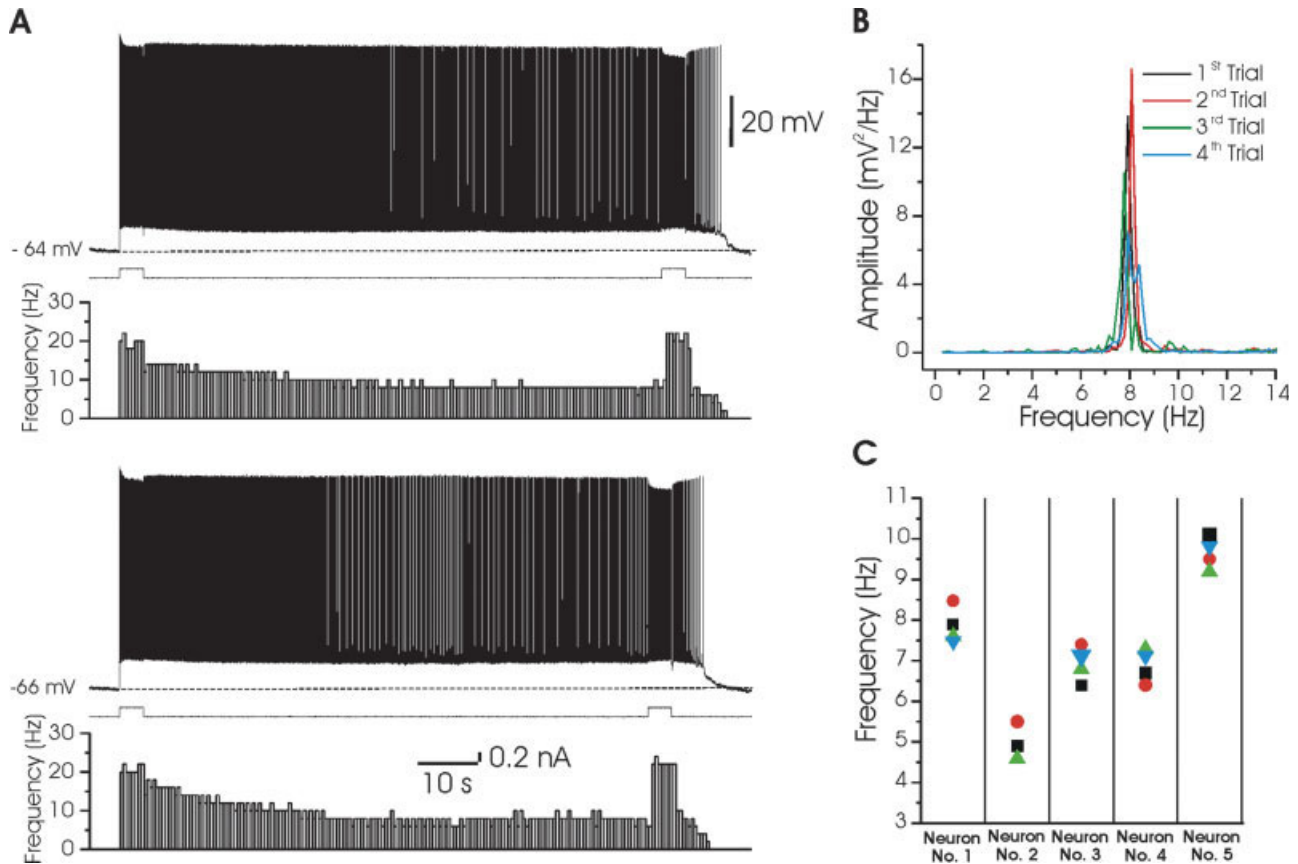


**FIGURE 1.** Muscarinic-mediated persistent activity in layer III LEC neurons. In this Figure and all the subsequent figures, recordings were performed with continuous bath perfusion of carbachol (10  $\mu$ M). **A:** Induction of persistent activity is voltage dependent. Left: membrane potential (upper trace) recorded during current injection (lower trace) that shows the spiking response to depolarizing steps at different membrane potentials. Note that persistent spiking activity appears after the depolarizing step at the highest baseline potential (at this low temporal resolution, spiking appears as solid blocks). Right: plot of plateau potential amplitude vs. baseline membrane potential in five different recorded neurons (different colors and symbols for different neurons). Most neurons show persistent activity (P) after current steps from baseline over  $\sim -68$  mV. **B:** Duration of step depolarization current pulse has a strong influence on the duration of the plateau potential and post-stimulus spiking. Left: membrane potential and associated current

traces during stimulus pulses of 0.5, 1, 2, 4 (top) and 8 and 16 s duration (bottom). Persistent spiking appears after the 4-s pulse. Post-stimulus spiking terminates soon after 8 and 16 s pulses. Right: Plot of plateau (or post-stimulus spiking) duration vs. stimulus duration in six different recorded neurons. All neurons show persistent activity (P) after 4-s pulses, and some neurons show the persistent activity after 2 and 8 s pulses. Different colors and symbols represent different neurons. **C:** Persistent activity is mediated through muscarinic receptors. Membrane potential and associated current traces in carbachol condition (left traces) and after addition of atropine (right traces). Under our regular CCh conditions, a step depolarizing current pulse is followed by a depolarizing plateau potential (PP, arrow) and persistent firing that was fully blocked after addition of atropine (1  $\mu$ M) to the bath solution. Right, Bar graph shows the mean  $\pm$  SE amplitude of the PP recorded under both conditions (\*\*\*) denotes  $P < 0.001$ ;  $n = 4$ ).

The observations that in layer III LEC neurons the post-stimulus spiking was self-terminating after application of a prolonged suprathreshold depolarizing current pulse (longer than 8 s) suggest that the persistent activity in these neurons under-

goes a desensitizing or adapting process during prolonged depolarization. Thus, we decided to test the effect of application of a second depolarizing current pulse during the persistent activity. As illustrated in Figure 2A, we observed that in a major-



**FIGURE 2.** Switching “On” and “Off” persistent activity in layer III LEC neurons. **A:** Two typical recordings of membrane potential, current traces and the corresponding peri-stimulus spiking rate histogram (bin width = 500 ms) for a layer III LEC neuron. **B:** Power spectrum plot for the persistent activity of the same neuron shown in **A** for four different trials. Note there is a clear peak for a

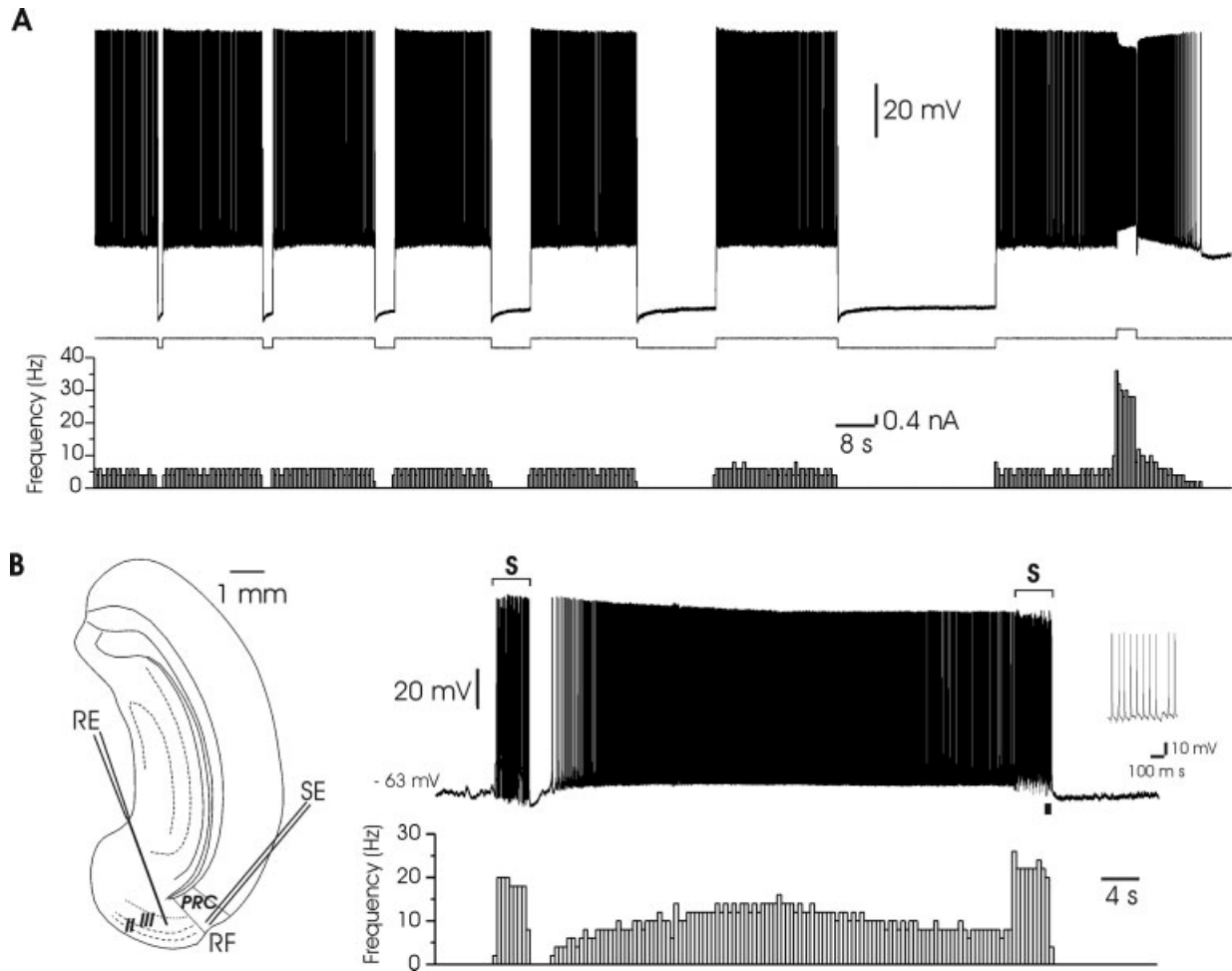
specific frequency in different trials. **C:** Frequency of persistent activity is plotted for five different neurons in which “On” and “Off” states were repeated for several trials. Different colored symbols represent different trials for each individual neuron. While individual neurons show strong frequency specificity during sustained activity, the group of neurons displays frequencies that cover the theta range.

ity of recorded neurons ( $\sim 70\%$  of total recorded neurons;  $n = 41$ ), application of a second 4-s pulse, identical to the first pulse, was sufficient to terminate the persistent activity with a delay of  $6.28 \pm 0.45$  s (range 0–15.6 s) after termination of the second depolarizing pulse (a movie of this effect is available at <http://people.bu.edu/hasselmo/babakcell.mpg>, which shows an oscilloscope display of the membrane potential of a single layer III LEC neuron during switching “On” and “Off” of persistent spiking activity with step depolarizing pulses). The ability to switch the persistent spiking activity “On” and “Off” in these neurons was a robust phenomenon since it was repeatable as long as recordings were maintained. However, in some cases ( $\sim 25\%$  of total recorded neurons;  $n = 16$ ) longer duration pulses (6–10 s) or current pulses with higher intensity (0.1–0.2 nA more than the first pulse) were necessary to terminate the persistent activity. We were not able to turn off the persistent activity in three recorded neurons even with longer or stronger pulses.

We measured that in neurons with the “On/Off” ability the first (“On”) and second (“Off”) 4-s depolarizing pulses triggered action potentials with significantly different frequencies. The mean frequencies were  $21.03 \pm 0.47$  Hz for the “On” pulse and

$23.76 \pm 0.52$  Hz for the “Off” pulse ( $P < 0.001$ ;  $n = 64$ ). For these neurons, mean frequency during the period of persistent spiking was ( $6.61 \pm 0.24$ ) Hz (range 3.1–12.6 Hz). Interestingly, we observed that there is a very strong frequency specificity for each individual neuron (Fig. 2B). Multiple tests in a single neuron induced persistent spiking with approximately the same firing frequency for that neuron. However, different neurons in the population of neurons in layer III of the LEC are able to generate persistent activity at frequencies that cover the theta range (ranging from 3 to 12 Hz) (Fig. 2C). We also observed that if step depolarizing current pulses were sufficient to trigger persistent spiking activity, frequency specificity of the persistent activity for each individual neuron was independent of the baseline membrane potential (Fig. 2A) or the intensity of the pulse (data not shown).

We also investigated the effect of step hyperpolarizing current pulses at variable durations and intensities on persistent spiking activity evoked by prior depolarizing current pulses in these neurons. Our data indicated that application of step hyperpolarizing currents with different duration (Fig. 3A; range 0.5–30 s;  $n = 8$ ), or different intensities (range 0.05–0.5 nA;  $n = 3$ ; data not shown) is ineffective to either reduce or



**FIGURE 3.** A: Persistent activity in layer III LEC neurons is resistant to a hyperpolarizing current pulse. Upper trace shows membrane potential of a neuron that previously received input inducing persistent spiking. The membrane potential is shown during a series of hyperpolarizing current injections (middle trace) of different durations (up to 32 s in this case). A peri-stimulus spike rate histogram (bin width = 500  $\mu$ s) is shown at bottom indicating that the hyperpolarizing pulses can not reduce the frequency of the persistent activity or terminate it. However a step depolarizing pulse (at far right) was able to switch "Off" the persistent activity. Final membrane potential is  $-60$  mV. B: Switching "On" and "Off" persistent activity by synaptic stimulation. In these experiments no synaptic

blockers were presented ( $n = 6$ ). Left: schematic diagram shows locations of stimulating (SE) and recording (RE) electrodes in the slice preparation. RF and PRC represent rhinal fissure and perirhinal cortex, respectively. Right: membrane potential trace and peri-stimulus spike rate histogram (bin width = 500 ms) showing induction and termination of the persistent activity in layer III LEC neuron by synaptic activation of PRC superficial layers. Inset corresponds to the section indicated by the black bar (below) showing generation of postsynaptic excitatory potentials and accompanying action potentials in layer III LEC neuron following synchronized electrical stimulation of the PRC at larger time scale. For clarity, stimulus artifacts are removed. S represents period of synaptic stimulation.

change the frequency of the persistent spiking activity in all tested neurons. However, a very prolonged hyperpolarizing current pulse (above 40 s) can be effective to cease the persistent activity (three out of three tested neurons). Thus, persistent activity in these neurons is insensitive to the hyperpolarizing pulse (up to 30-s pulses); however as depicted in Figure 3A, the evoked persistent activity still has the ability to be turned "Off" by application of a depolarizing pulse.

Since the "On" and "Off" states of the persistent activity seem to be robust phenomena among the population of layer III LEC principal neurons, in the next step we wanted to test if induction and termination of persistent activity in these neurons was also achievable by synchronized synaptic activation. These neurons

are the main targets of superficial cell layers of the perirhinal cortex (Burwell and Amaral, 1998b), and electrophysiological evidence has already shown that electrical stimulation of layers II/III of the perirhinal cortex evokes mono-synaptic excitatory postsynaptic potentials with the probability of triggering action potentials in layer III LEC neurons (de Villers-Sidani et al., 2004). Figure 3B shows a schematic diagram showing the locations of stimulating and recording electrodes in our slice preparation. These experiments were performed in the absence of kynurenic acid and picrotoxin. Figure 3B illustrates (left trace) a typical initiation and termination of the muscarinic mediated persistent spiking activity in a layer III LEC neuron following synchronized electrical stimulation of the PRC layers II/III. While we were able easily to

initiate persistent activity with synaptic stimulation in all tested neurons (stimulus frequency 15–20 Hz; stimulus intensity 200–300  $\mu$ A; stimulus duration 4 s;  $n = 6$ ), we recognized that termination of the persistent activity through synaptic activation required higher intensity electrical stimulation (400–500  $\mu$ A, stimulus duration 4 s;  $n = 6$ ). With higher intensity stimulation, we were able to terminate the persistent activity in all but one neuron with synaptic stimulation.

## DISCUSSION

In this study, we demonstrated that individual neurons in layer III of the LEC are able to switch “On” and “Off” their persistent spiking activity due to depolarizing inputs including both intracellular current injection and synaptic stimulation. The effect depends upon muscarinic receptor activation, as it was observed in the presence of the nonselective cholinergic agonist carbachol and was blocked by the muscarinic antagonist atropine. Data presented show that activity-dependent post-stimulus spiking in layer III depends on the baseline membrane potential voltage, and also depends on the duration of the excitatory depolarizing stimuli. We observed that short excitatory stimuli (0.5 and 1 s) are not sufficient to induce persistent activity. Furthermore, very prolonged duration current stimuli (8 and 16 s) also induce self-terminating post-stimulus spikes. However, stimuli with moderate duration (4 s) are sufficient to induce post-stimulus spikes that usually generate persistent activity.

Previous studies showed muscarinic- and activity-dependent post-stimulus spikes in principal neurons of layer II (Klink and Alonso, 1997; Magistretti et al., 2004) and layer V (Egorov et al., 2002; Fransen et al., 2006) of the medial EC (MEC). It has been shown that in layer II MEC principal neurons the post-stimulus spikes are always self-terminating and can last only up to a couple of tens of seconds ( $15.24 \pm 0.97$  s and  $29.52 \pm 7.57$  s) for pyramidal and stellate neurons, respectively (Magistretti et al., 2004). In contrast to those data, our data in layer III of the LEC show the existence of post-stimulus spiking which persists almost for an indefinite period of time (tested for many minutes). Graded persistent activity has been observed in single principal neurons of layer V of the MEC (Egorov et al., 2002; Fransen et al., 2006). In those neurons, it has been shown that the frequency of the persistent activity is able to be graded up and/or down depending on the nature of the stimuli and that a longer duration suprathreshold depolarizing pulse induces persistent activity at higher frequency in comparison with the frequency that is induced with a shorter duration pulse (Fransen et al., 2006). In contrast to the graded persistent activity, our current studies clearly show that layer III neurons can generate neither graded persistent activity nor persistent activity at a higher frequency following application of a prolonged step depolarizing current pulse.

We also observed that each individual layer III LEC principal neuron has very pronounced frequency specificity, which can be induced in repeated tests, and that the different frequencies of persistent activity for different neurons in the popula-

tion of cells cover the theta frequency band. More interestingly, our data also indicate that the persistent activity in these neurons, in most cases, can be terminated following application of a second excitatory stimulus identical in intensity and duration to the first stimulation. Thus, the persistent activity in these neurons is able to toggle between two reliable states, one a state of persistent spiking activity (“On”) and the other a silent (“Off”). In this respect these neurons can behave like a toggle switch by turning “On” and “Off” the activity-dependent persistent spiking activity during muscarinic receptor activation. Furthermore, the persistent activity in these neurons can not be terminated by application of hyperpolarizing pulses. Switching “On” and “Off” the persistent activity in layer III neurons could be a plausible physiological mechanism involved in memory function, since we were able to induce and terminate persistent spiking by synaptic activation of superficial cell layers of the perirhinal cortex. Taken together, these data indicate that information in terms of persistent activity can be transferred easily between the LEC and PRC. This is consistent with neurophysiological, anatomical and lesion studies that indicate explicitly the importance of the integrity of the EC and highly interconnected adjacent cortical regions in the communication between the neocortex and the hippocampus upon which long-term memory formation depends (reviewed in Buzsaki, 1996).

Recent studies have also shown that neurons in other brain areas can switch “On” and “Off” their electrical activity (Shu et al., 2003; Loewenstein et al., 2005). Loewenstein et al. (2005) showed the transition of the cerebellar purkinje cells in an *in vivo* preparation between hyperpolarized (“Down State”) and stable depolarized states (“Up State”). In contrast to our findings; however, in that study termination of depolarized states was triggered by hyperpolarizing pulses. Turning “On” and “Off” the balance of recurrent synaptic activity has been observed in *in vitro* prefrontal cortex circuits (Shu et al., 2003). That study showed how cortical “Up-states” and “Down-states” can be generated by a barrage of synaptic inputs in ferret slices in a modified extracellular ring solution. That mechanism does not contradict the parallel intrinsic mechanism suggested here. Our intrinsic mechanism would add to the stability of network function. It is worthy to note that in those experiments the duration for each stable state was at most a couple of seconds. However, the intrinsic mechanism presented here would allow the network to maintain “Up-states” for expected periods of many seconds or minutes consistent with behavioral time-scales.

The mechanisms for sustained activity described here could play an important role in maintaining working memory for sensory stimuli in delayed match-to-sample tasks, and could also enhance encoding into long-term memory. This intrinsic mechanism for persistent spiking could underlie the delay period spiking observed during performance of delayed match and delayed nonmatch to sample tasks in rats and monkeys (Suzuki et al., 1997; Young et al., 1997). The dependence of persistent spiking on cholinergic modulation is consistent with cholinergic blockade impairing performance on delayed match-to-sample tasks (Penetar and McDonough, 1983). Because these intrinsic cellular mechanisms allow persistent spiking without prior synaptic

modification, it could be particularly important for maintenance of novel stimuli. This is consistent with data showing that selective lesions of the cholinergic innervation of EC selectively impair delayed non match-to-sample function for novel but not familiar odors (McGaughy et al., 2005). In human subjects, maintenance and encoding of novel stimuli in a delayed match-to-sample task correlates with entorhinal and perirhinal activity during the delay period, as measured using fMRI (Schon et al., 2004), and this delay period activity is reduced by muscarinic blockade with scopolamine (Schon et al., 2005). Thus, persistent activity provides an important mechanism of working memory for novel stimuli (Hasselmo and Stern, 2006).

While persistent activity is important for working memory, it requires mechanisms for termination of activity associated with repeated sequences of sensory input, to allow effective representation of new relations between events during an episode. These mechanisms for termination could be particularly relevant to experimental data on neural activity during delayed match to sample tasks (Suzuki et al., 1997). In this task, the subject must: (1) maintain memory of the sample stimulus during the delay period but not the inter-trial interval, (2) ignore intervening nonmatch distractors, (3) generate a response to the final stimulus (match stimulus), and finally (4) forget during the inter-trial interval in order to prepare for a new sample stimulus on the next trial. The neural properties described here provide a cellular mechanism useful for this task. As shown here, the spiking activity associated with the sample will resist hyperpolarization caused by lateral inhibition induced by presentation of distractor stimuli during the delay period. When the test stimulus appears again as a match stimulus, the response can be generated, and the repetition would shut off persistent activity, allowing the system to respond to a new sample stimulus. This indicates the functional importance not only in the ability to activate persistent spiking, but in the ability of synaptic activation to toggle neurons between the plateau state and the resting state.

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