Effect of dendritic location and different components of LTP expression on the bursting activity of hippocampal CA1 pyramidal cells

Gergely Papp [a,*], Máté Lengyel [a], Péter Érdi [a,b]

[a] *Dept. Biophysics, KFKI R.I.P.N.P., Hungarian Academy of Sciences, 29-33 Konkoly Thege M.. út, Budapest H-1121, Hungary*

[b] *Center for Complex Systems Studies, Kalamazoo College, 1200 Academy street, Kalamazoo, MI 49006-3295, USA*

Abstract

In recent *in vivo* experiments individual hippocampal CA1 pyramidal cells changed their bursting activity disparately in response to LTP induced by stimulation in area CA3. We investigated that the LTP of which synapse system (CA3 recurrents or Schaffer collaterals) and which component of LTP at CA1 pyramidal cells (an increase in synaptic currents, a decrease in feed-forward inhibition, or an increase in voltage-dependent calcium currents) is responsible for these disparate effects. We found that only insertion of new calcium channels may lead to experimentally observed changes in bursting activity. In line with *in vitro* experimental findings, LTP in the basal dendrite resulted in a higher degree of potentiation than in the apical dendrite, which was accounted for by morphological differences between the two dendritic regions.

Key words: E-S potentiation, calcium channel, inhibition, CA3, model

1 Introduction

Several experimental and modeling works support the hypothesis that the mechanism of memory trace formation at the cellular level is long-term potentiation (LTP) and long-term depression (LTD) [6]. Two components of LTP/D are known: expression of the synaptic component leads to enlarged/reduced EPSPs, while expression of the EPSP-Spike (E-S) component results in increased/decreased probability of firing at a constant EPSP amplitude. Long term plasticity is known to occur at different synapses throughout the hippocampus [6]. However, it is still unclear that the plasticity in which synapse system is of crucial importance and which of its components are expressed during learning at the behavioral level.

Recently, *in vivo* experiments on hippocampal LTP in anesthetized animals led to unexpected results [7]. Pyramidal cells in CA1 changed their bursting activities disparately after LTP was induced by theta burst stimulation in the CA3 region: some of the cells increased while others decreased their spontaneous firing frequencies. Changes in evoked firing following potentiation showed a similar pattern and there was also no correlation with changes in spontaneous activity. To elucidate these findings we investigated how the spontaneous firing pattern of a CA1 pyramidal cell changed depending on where LTP was induced (in CA3 recurrent synapses or in synapses formed by the Schaffer-collaterals) and which of its components was expressed (synaptic or E-S).

* Corresponding author.
Email address: pgergely@rmki.kfki.hu (Gergely Papp).

2 Materials and methods

In our computer simulations an experimentally validated multicompartmental model of a CA1 pyramidal cell [8] was used.

CA3 pyramidal cells were not modeled explicitly, only their postsynaptic effects on the modeled CA1 cell were taken into account through 1-1 AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole-proprionic acid) synapse ($\tau = 2\,\mathrm{ms}$, $g_{\max} = 10\,\mathrm{nS}$, $E_{\mathrm{rev}} = -10\,\mathrm{mV}$) impinging the apical and basal dendrite at $480\,\mu\mathrm{m}$ and $440\,\mu\mathrm{m}$ from the soma, respectively. Ensemble spike trains of presynaptic CA3 cells had a mean frequency 100 Hz. Local, perisomatic inhibition on the CA1 cell was modeled with a single $\mathrm{GABA_A}$ (γ-aminobutyric acid) synapse ($\tau = 7\,\mathrm{ms}$, $g_{\max} = 10\,\mathrm{nS}$, $E_{\mathrm{rev}} = -75\,\mathrm{mV}$) impinging the somatic compartment, receiving a 50 Hz (mean frequency) presynaptic spike train frequency modulated sinusoidally at theta frequency (10 Hz) between $0 - 100\,\mathrm{Hz}$. Presynaptic spike trains were in all cases generated by changing parameter Poisson processes, parameterized with instantaneous presynaptic firing frequencies, and then were convolved with alpha-function postsynaptic conductance-change waveforms [2] (see parameters above).

The effect of LTP was modeled in one of four ways. (1) LTP in CA3 recurrent collaterals was modeled as an increase in the synchrony of presynaptic spike trains, leaving mean CA3 firing activity unchanged [3]. The distribution of possible instantaneous firing frequencies in the presynaptic CA3 ensemble spike train was tight unimodal before LTP, and became bimodal following LTP expression (Fig. 1). Three components of LTP in CA3→CA1 Schaffer collaterals were modeled. (2) Synaptic component of LTP was modeled as an

increase in the maximal conductance of excitatory AMPA channels (Fig. 2). Two potential sources of E-S potentiation were taken into account: (3) a decrease in feed-forward inhibition as a decrease in the maximal conductance of the $GABA_A$ channel (Fig. 3), and (4) the insertion of new, functional Ca^{2+}channels into the cell membrane as an increase in the maximal conductance of voltage-dependent Ca^{2+}-channels (4).

A burst was defined as a series of at least 3 consecutive spikes separated by less then 13 ms interspike intervals (ISI) [4]. Firing pattern of the model cell was characterized by bursting frequency (number of bursts per second) and burstiness (number of intraburst spikes divided by the number of all spikes). Statistics were calculated from 12 (Figs. 4 and 5: 10) parallel runs with the same parameters but different random presynaptic spike trains, each 10 s (Figs. 4 and 5: 15 s) long with the first 1 sec discarded to omit transient behavior. Error bars show standard deviation. Simulation time step was 2.5 μs.

3 Results

LTP expressed in the recurrent collaterals of CA3 pyramidal cells, if potentiated cells projected to the basal dendrite of the CA1 cell (Fig. 1B) increased both bursting frequency and burstiness slightly. If potentiated cells projected to the apical dendrite (Fig. 1A), the increase in both characteristics remained insignificant (no formal significance test was applied).

Synaptic component of LTP in CA1 increased both bursting frequency and burstiness in both dendrites (Fig. 2A and B), the increase was again greater when LTP was expressed at the basal dendrite.

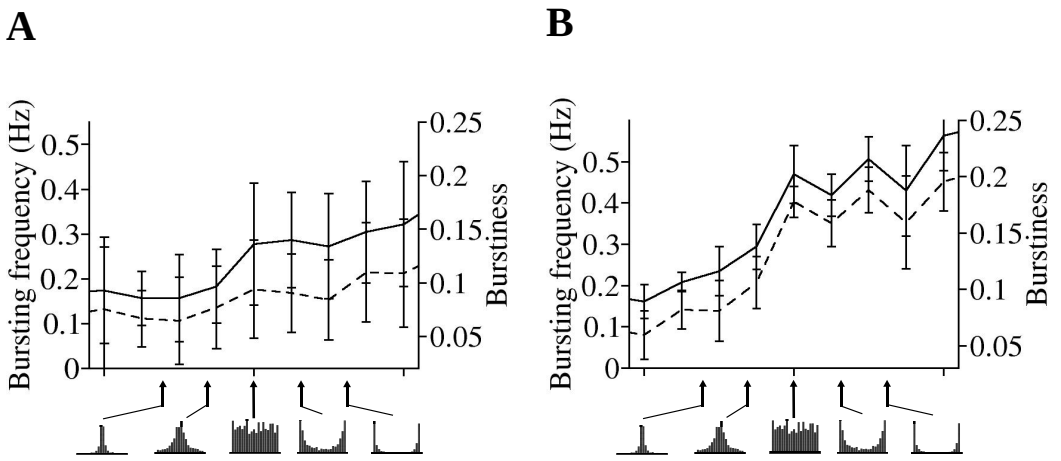

Fig. 1. . LTP in the CA3 recurrent network. Bursting frequency (left y-axis, solid line) and burstiness (right y-axis, dashed line) as a function of synchrony in CA3 firings if potentiated CA3 cells projected to the apical (A) or basal (B) dendrite. Insets on the x-axis show instantaneous firing frequency histograms of presynaptic ensemble spike trains. (Inset x-axis: firing frequency between $0 - 200\,\mathrm{Hz}$, y-axis: relative frequency.)

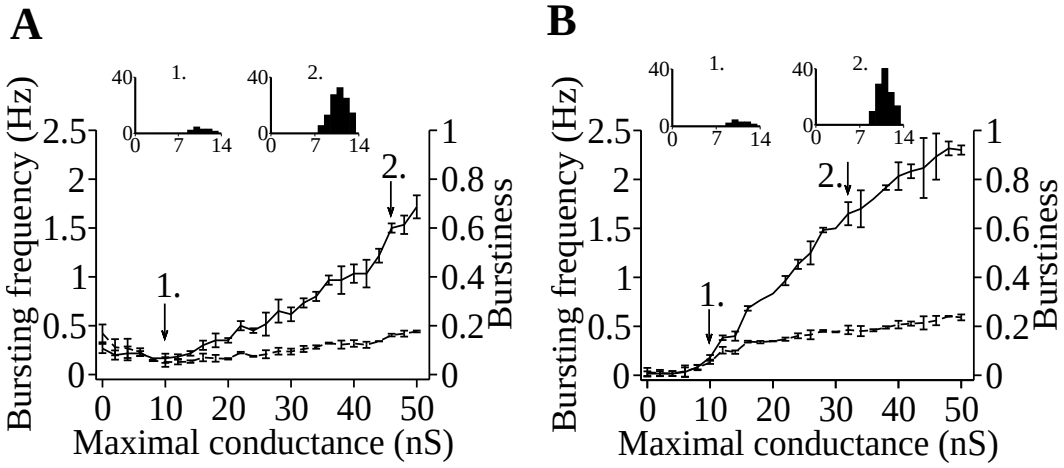

Fig. 2. Synaptic component of LTP in CA1. Bursting frequency (left y-axis, solid line) and burstiness (right y-axis, dashed line) as a function of maximal AMPA conductance in the apical (A) or basal (B) dendrite. Arrows with label 1 show initial values of maximal synaptic conductance (before LTP). Insets show intraburst ISI histograms at maximal AMPA conductance values indicated by arrows, x axis: time (ms), y axis: relative frequency (count).

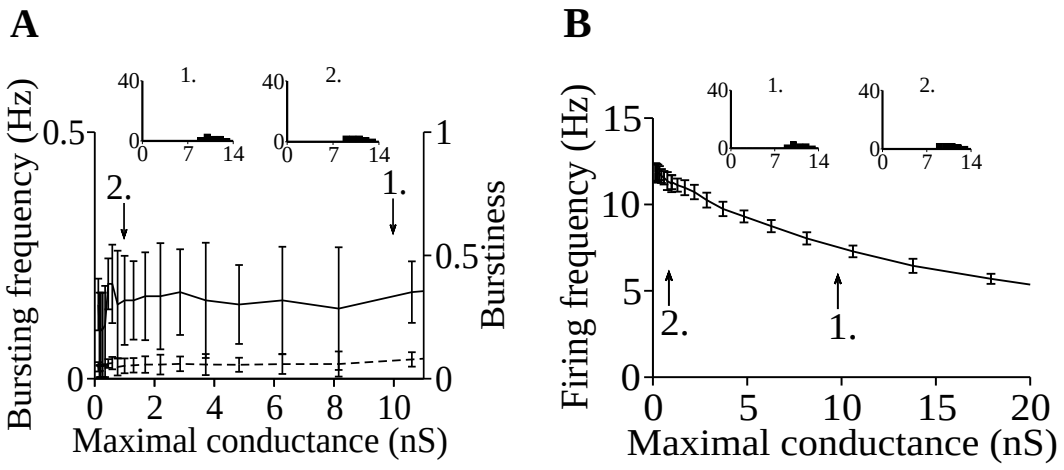

Fig. 3. E-S component of LTP in CA1: decreasing inhibition. Bursting frequency (A, left y-axis, solid line), burstiness (A, right y-axis, dashed line) and firing frequency (B) as a function of maximal $GABA_A$ conductance. Arrows with label 1 show initial values of maximal synaptic conductance (before LTP). Insets show intraburst ISI histograms at maximal $GABA_A$ conductance values indicated by arrows, x axis: time (ms), y axis: relative frequency (count).

According to our earlier results [5], decreasing feed-forward inhibition (as a possible mechanism of E-S potentiation in CA1) affected only spike firing frequency (Fig. 3B) but left bursting unaltered (Fig. 3A).

Modeling the insertion of new functional voltage-dependent Ca^{2+} channels led to disparate effects: insertion in apical or basal synaptic compartments (Fig. 4A and B) resulted in robust increase of bursting frequency and burstiness, while increasing Ca^{2+} in the somatic compartment resulted in an opposite effect: it virtually eliminated bursting (Fig. 4C). Further, when maximal conductance of Ca^{2+} channels was only slightly increased, it reversed the effect on bursting in every case: it led to a small depression in proximal compartments and to minor potentiation in perisomatic compartments (data not shown). At higher values of Ca^{2+} conductance, strong LTD at proximal and robust LTP at distal sites was seen. The change was, however, larger at distal basal

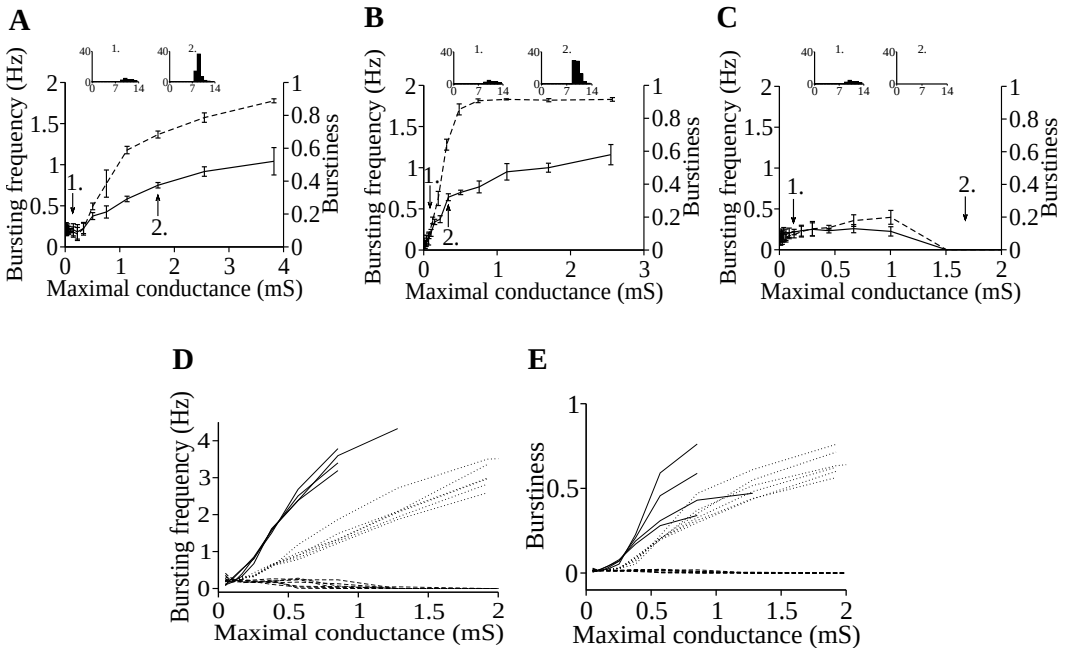

Fig. 4. E-S component of LTP in CA1: insertion of new functional Ca^{2+} channels into the cell membrane. A,B,C: Bursting frequency (left y-axis, solid line) and burstiness (right y-axis, dashed line) as a function of increasing maximal Ca^{2+} conductance in the compartments where apical (A) or basal (B) synapses impinge or in the somatic (C) compartment. Arrows with label 1 show initial values of maximal Ca^{2+} conductance (before LTP). Insets show intraburst ISI histograms at maximal Ca^{2+} conductance values indicated by arrows, x axis: time (ms), y axis: relative frequency (count). D,E: Bursting frequency (D) and burstiness (E) as a function of increasing maximal Ca^{2+} conductance in distal apical (dotted lines), distal basal (solid lines) or perisomatic including proximal apical and basal dendritic compartments (dashed lines).

locations (Fig. 4D, E).

Functional differences between the two main regions of the dendritic arbor were revealed in the model CA1 pyramidal cell: LTP in basal dendritic branches led to stronger enhancement of cellular activity than that in the apical (Figs. 1,2 and 4). To elucidate the source of this incongruity the basal dendrite was grad-

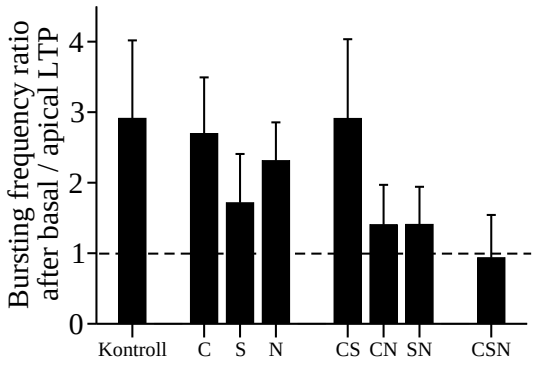

Fig. 5. Sources of functional differences between apical and basal dendritic regions. The basal dendrite was gradually transformed into being identical with the apical dendrite by changing active conductances (C), size (diameter and length, S) and the number (N) of basal dendritic compartments to values characterizing the apical dendrite. Bars show normalized bursting frequency after synaptic LTP is expressed in the basal dendrite relative to apical LTP expression following transformations indicated on the x-axis (control: without transformations). Dashed horizontal line indicates ratio of 1.

ually transformed into being identical with the apical dendrite by changing active conductances (C), size (diameter and length, S) and number (N) of basal dendritic compartments to values characterizing the apical dendrite. Changes in the effect of the synaptic component of LTP on bursting frequency at apical and basal dendritic sites was monitored. Our results showed that the difference in bursting frequency after LTP expression between the two dendrites decreased if size and number (SN) of compartments, or active conductances and number of compartments (CN) of the basal dendrite was set to values characteristic of the apical dendrite (Fig. 5). This difference disappeared if all three differing parameters (C, S, N) of the basal dendrite were set to the respective 'apical' values.

4 Discussion

Our results showed that only the insertion of new, functional Ca^{2+} channels into the cell membrane, a form of E-S potentiation, led to disparate effects in bursting activity of CA1 pyramidal cells similar to what was measured in experiments [7]: depending on the exact location (proximal vs. distal) and amount of increase in Ca^{2+} conductance bursting could be potentiated or depressed. This extends results of earlier studies demonstrating that the location of Ca^{2+} channel insertion influences the synapse-specificity of LTP [9].

What is the mechanism underlying the disparate effects of Ca^{2+} channel-based E-S potentiation? Bursting activity of pyramidal cells is determined by two counter-acting processes: Ca^{2+} influx channels depolarizes the membrane and enhances the occurrence and duration of bursts. Parallel to this, Ca^{2+}-dependent K^+ currents are activated and terminate bursts as well as increase interburst intervals by hyperpolarizing the membrane. Thus, increasing Ca^{2+} conductance may lead to different changes in bursting activity via shifting the balance between these two processes by different degrees at different loci on the dendrite.

In accordance with *in vitro* studies [1] (and G. P., B. Farkas, I. Világi, M. L., P. , unpublished observations) we found a fundamental difference between apical and basal dendrites, the latter showing significantly stronger potentiability (Figs. 1, 2 and 4). This distinction depended on morphological alterations between the two dendritic regions as it decreased in the SN and CN and disappeared in the CSN case (see Results and Fig. 5). This may be attributed to the shunting effect of additional compartments in the SN and CN cases de-

creasing currents reaching the soma from the transformed basal dendrite. In a previous experimental study, both morphological alterations and differences in the strength of inhibition between the two dendritic regions were implicated as possible sources for functional differences between apical and basal dendrite [1]. Our results support the hypothesis that morphological differences alone can account for this incongruity.

Acknowledgements

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References

[1] A. Arai, J. Black, G. Lynch, Origins of the variations in long-term potentiation between synapses in the basal versus apical dendrites of hippocampal neurons., Hippocampus 4 (1994) 1–10.

[2] J. M. Bower, D. Beeman, The book of GENESIS, TELOS, Springer-Verlag Publishers, New York, 1995.

[3] G. Dragoi, K. D. Harris, G. Buzsáki, Place representation within hippocampal networks is modified by long-term potentiation, Neuron 39 (5) (2003) 843–853.

[4] K. D. Harris, H. Hirase, X. Leinekugel, D. A. Henze, G. Buzsáki, Temporal interaction between single spikes and complex spike bursts in hippocampal pyramidal cells, Neuron 32 (1) (2001) 141–149.

[5] M. Lengyel, Á. Kepecs, P. Érdi, Location-dependent differences between somatic and dendritic IPSPs, Neurocomputing 26–27 (1999) 193–197.

[6] S. J. Martin, P. D. Grimwood, R. G. M. Morris, Synaptic plasticity and memory: an evaluation of the hypothesis, Annu Rev Neurosci 23 (2000) 649–711.

[7] P. D. Martin, M. L. Shapiro, Disparate effects of long-term potentiation on evoked potentials and single CA1 neurons in the hippocampus of anesthetized rats., Hippocampus 10 (2000) 207–211.

[8] R. D. Traub, R. K. S. Wong, R. Miles, H. Michelson, A model of a CA3 hippocampal pyramidal neuron incorporating voltage-clamp data on intrinsic conductances, J Neurophysiol 66 (1991) 635–649.

[9] J. C. Wathey, W. W. Lytton, J. M. Jester, T. J. Sejnowski, Computer simulations of EPSP-Spike (E-S) potentiation in hippocampal CA1 pyramidal cells., J Neurosci 12 (1992) 607–18.

Biosketches

Gergely Papp (born in 1980, Budapest, Hungary) received his M.Sc. degree in Cell-, Developmental and Neurobiology in 2003. He is starting his Ph.D. training in Cognitive Neuroscience at the International School for Advanced Studies (SISSA), Trieste, Italy. He has been working in Prof. Erdi's CNS group since 2002. He is interested building biologically realistic models of syanptic plasticity.

Máté Lengyel (born in 1975, Budapest, Hungary) received his M.Sc. degree in Cell-, Developemental and Neurobiology in 2000 and is finishing his Ph.D. training in Neurobiology in 2003 at Eötvös University of Sciences, Budapest. He has been working in Prof. Érdi's CNS group since 1995. He is modeling several hippocampus-related phenomena from the single cell to the network level.

Péter Érdi (born in 1946, Budapest, Hungary) received his Ph.D. in chemistry in 1981. He is the head of Department of Biophysics of the KFKI Research Instititue for Particle and Nuclear Physics of the Hungarian Academy of Sciences, and Henry R. Luce Professor at the Center for Complex Sytems Studies, Kalamazoo College, MI. His main scientific interest is computational modeling of the functional organization of the nervous system and other complex systems.