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Effects of dendritic location and different components of LTP expression on the firing activity of hippocampal CA1 pyramidal cells

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Several experimental and modelling 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) [4]. Two components of LTP/D are known: expression of the synaptic component leads to enlarged/reduced EPSPs (both in amplitude and in initial slope), 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 [4]. 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 anaesthetized animals led to unexpected results [3]: when LTP was induced by theta burst stimulation first in the contralateral then in the ipsilateral CA3 region, pyramidal cells in CA1 changed their bursting activities after both stimulations disparately: 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).

In our computer simulations two experimentally validated multicompartmental models of a CA1 cell were used [5, 6]. The two models differed both in morphology and in the exact composition of voltage dependent channels to test the robustness of our results against details at these respects. Morphological differences between the apical and basal dendritic regions were incorporated in both models. The models contained two types of synaptic currents: excitatory AMPA both in the basal and in the apical dendritic compartments corresponding to Schaffer-collateral synapse localization, and inhibitory $GABA_A$ perisomatically. The effect of LTP was modelled in one of four ways. (1) LTP of CA3 recurrent collaterals was modelled as an increase in the synchrony of presynaptic spike trains. Three components of LTP at the Schaffer-collaterals were modelled: (2) the synaptic component was modelled as an increase in the AMPA current, and two sources of the E-S component were taken in account: (3) the insertion of new, functional calcium-channels into the cell membrane as an increase in the voltage-dependent calcium-current, and (4) the decrease in feed-forward inhibition as a decrease in the $GABA_A$ current. Bursting activity of our model cell was characterized by two parameters: burst-frequency (number of bursts in a second) and burstiness (fraction of intraburst to all spikes).

Our results showed, that LTP occuring at CA3 recurrent synapses increased burst-frequency but left burstiness unaltered. If potentiated CA3 cells projected to the basal dendrite only, changes in both parameters were small, but in case of burst-frequency significant, while if they projected to the apical dendrite, the increase in both parameters were insignificant.

Synaptic component of LTP increased both burst-frequency and burstiness in both dendrites, the increase was again greater when LTP was expressed at the basal dendrite. When changes were applied at both synapses, an increase in maximal conductance of both excitatory synapses led to an increase in burst-frequency. However, for intermediate values of the basal synaptic conductance (10-29 nS) an increase in the apical synaptic conductance caused a transient decrease in burstiness; burstiness increased steadily as the maximal conductance of the basal synapse was increased.

According to earlier results [2], a decrease in feed-forward inhibition, that is decreasing the maximal conductance of the $GABA_A$-channel, changed only spike firing frequency by increasing it but left bursting properties unaltered. However, investigations over a larger parameter regime revealed a slight transient increase in bursting properties at higher maximal conductances of the $GABA_A$ current.

Modelling the insertion of new, functional voltage-dependent calcium-channels into the cell membrane led to disparate effects. On one hand, a small increase in the maximal conductance of calcium channels in the soma or in perisomatical compartments led to LTP, whereas in distal

compartments LTD was observed. On the other hand, at higher values of maximal calcium conductance, strong perisomatic LTD and strong distal LTP was found. Changes in bursting thus depended on where and how many new channels were inserted. Our results can be explained by that bursting is a result of two antagonistic processes: inward calcium current enhances both bursting through prolonging depolarization and the termination of bursts via activating outward calcium dependent potassium currents. As calcium dependent potassium currents are stronger perisomatically, enhancing calcium currents in perisomatic compartments results in a decrease of burst-activity whereas in distal compartments bursting is increased. Enhancement of calcium currents seems therefore to be a possible explanation for the disparate effects observed by Martin and Shapiro [3]. Again, LTP at distal basal dendrites yielded a larger increase in burst-frequency and in burstiness.

Moreover, functional differences between the two main regions of the dendritic arbor were revealed: in accordance with *in vitro* experiments [1], LTP in basal dendritic branches led to higher alterations in cellular activity than that in the apical. After gradually transforming the basal dendrite into an apical by changing active conductances, diameter, length and the numbers of basal dendritic compartments to values characterizing the apical dendrite, synaptic component of LTP at either dendrites led to the same amount of potentiation. Our findings thus indicate that this incongruity is most likely to be accounted for by morphological differences in CA1 pyramidal cells.

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