Computational models of homeostatic synaptic and dendritic plasticity in the hippocampus

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Abstract

I present our recent work on homeostatic aspects of (1) synaptic and (2) dendritic plasticity: (1) We used biologically realistic models of dentate granule cells to simulate LTP and heterosynaptic LTD observed in the hippocampal dentate gyrus. LTP and LTD could be accounted for by a combination of a spike-timing-dependent plasticity (STDP) mechanism and a fast homeostatic Bienenstock-Cooper-Munro (BCM)-like metaplasticity mechanism. (2) We used biologically realistic models of dentate granule cells to simulate functional consequences of denervation-induced dendritic plasticity. Our results showed that dendritic retraction boosted the excitability of denervated neurons and their responsiveness to synaptic stimulation, contributing to firing rate homeostasis.[1]

1 Introduction

Long-term strenghtening or potentiation (LTP) and long-term weakening or depression (LTD) of synapses are key mechanisms of learning and memory. Hippocampal dentate gyrus plays an important role in spatial learning. In our recent work we focused on homeostatic aspects of (1) synaptic and (2) dendritic plasticity in the dentate gyrus:

(1) Synaptic plasticity in the form of long-term potentiation (LTP) and long-term depression (LTD) is widely accepted to underly synaptic changes involved in the storage and processing of information in the hippocampus. It remains uncertain, however, which particular activity rules are utilized by hippocampal neurons to induce LTP and LTD in behaving animals. Recent experiments in the dentate gyrus of freely moving rats (Bowden et al., 2012) revealed an unexpected pattern of LTP and LTD from high-frequency perforant path stimulation. While 400 Hz theta-burst stimulation (400-TBS) and 400 Hz delta-burst stimulation (400-DBS) elicited substantial LTP of the tetanized medial path input and, concurrently, LTD of the non-tetanized lateral path input, 100 Hz theta-burst stimulation (100-TBS, a normally efficient LTP protocol for in vitro preparations) produced only weak LTP and concurrent LTD. The results show that a simple STDP plasticity rule with fast BCM homeostasis / metaplasticity can reproduce the Bowden et al. pattern of results when implemented in a compartmental granule cell model with realistic biophysics. The model thus gives insight into the computations that granule cells are making, as driven by plasticity-inducing synaptic events arising from both tetanization and background activity (see below).

(2) In contrast to synaptic plasticity, structural plasticity of dendrites is a much less studied and understood form of neuronal plasticity. Therefore, in the second part of my presentation, I describe anatomically detailed models of hippocampal neurons, which predict that dendritic plasticity is able to homeostatically adjust neuronal excitability and possibly modulate local synaptic plasticity. In our modeling we focused on denervation-induced dendritic plasticity. The phenomenon of denervation-induced dendritic plasticity has been studied in some detail using the classical "entorhinal cortex lesion (ECL) model" (see e.g. Deller & Frotscher, 1997). In this experimental setting entorhinal afferents to dentate granule cells are lost and granule cells profoundly remodel their dendritic tree (e.g. Vuksic et al., 2011). Entorhinal denervation causes a loss of dendrites of dentate granule cells resulting in less complex dendritic arbors and a persistent shortening of the dendritic tree. The functional consequences of this shortening or retraction, which typically have been regarded as "atrophic", damaging or detrimental to the denervated neuron, have not been studied and remained elusive.

(1) & (2): In the discussion I suggest that future studies should be exploring how synaptic and dendritic plasticity interact with each other.

2 Results

(1) To simulate heterosynaptic plasticity, we adopted a published, multicompartmental and biophysically realistic computational NEURON model of a dentate gyrus granule cell (Aradi and Holmes, 1999; Santhakumar et al., 2005). This nine-section, 125 compartment granule cell model received input from 150 medial path synapses and 150 lateral path

[1] Parts of this presentation have been previously published by PLOS Computational Biology and Acta Neuropathologica Communications in open access articles (Jedlicka et al., 2015; Platschek et al., 2016) under the Creative Commons Attribution License 4.0, which permits unrestricted use, distribution, and reproduction.

synapses, distributed in appropriate zones across the two dendritic branches (Fig. 1).

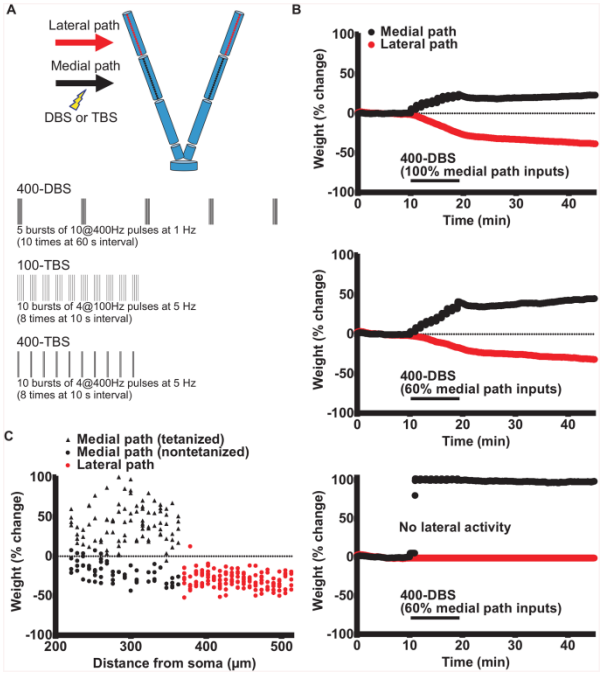

Fig. 1: Biophysically realistic granule cell model for generating LTP on the medial path and concurrent LTD on the lateral path (Jedlicka et al., 2015).

The schematic in Fig. 1A shows the compartmental model. Red and black dots on the dendrites represent positions for medial and lateral perforant path synapses, respectively. Three HFS protocols applied to the medial path were used to test for LTP on the medial path and concurrent LTD on the lateral path: 400-DBS, 100-TBS and 400-TBS (Fig. 1A, bottom). Panel B in Fig. 1 shows perforant path synaptic weights on a simulated granule cell before, during and after 400-DBS of the medial perforant path. Top: 400-DBS delivered to all medial path synapses produced smaller LTP on the medial path than concurrent LTD on the lateral path. Middle: 400-DBS delivered to 60% of medial path synapses produced greater LTP than concurrent LTD. Bottom: There was a loss of lateral path LTD when ongoing activity in that pathway was set to zero after the onset of 400-DBS (no lateral activity), demonstrating the need for ongoing spontaneous synaptic activity to drive LTD in the non-tetanized synapses. All graphs depict average values for all given synapses over 3 runs. Panel C in Fig. 1 shows spatial distribution of synaptic weight changes for 400-DBS delivered to 60% of medial path synapses, showing that non-tetanized medial synapses exhibit LTD. Weight changes are expressed as % change with respect to their baseline value.

The model was endowed with a synaptic plasticity mechanism containing a presynaptically centered nearest-neighbor implementation of the STDP rule with fast homeostasis (metaplasticity). The multicompartmental granule cell model included the biophysics of the main ion channels in the dendrites and soma. Action potentials were generated in the soma and back-propagated along the dendrites, both electrotonically as well as due to the action of dendritic sodium and calcium ion channels. Thus the granule cell model took into account all of the complex spatio-temporal integration of EPSPs in the dendrites that are evoked by the spontaneous activity, the experimental high-frequency stimulation (HFS) protocol, and the back-propagating postsynaptic spikes. In addition, we employed a realistic simulation of the granule cell spontaneous input activity according to in vivo data that show a significant peak around 8 Hz for both the medial and lateral pathways.

Figure 2 summarizes the plasticity results generated by the compartmental model, and compares them with the experimental data obtained by Bowden et al. (2012).

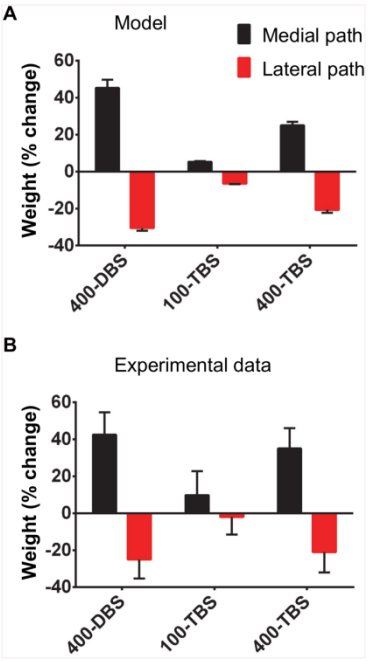

Fig. 2: Summary of effects of stimulation pattern on LTP and concurrent LTD in compartmental model simulations and experiments (Jedlicka et al., 2015).

400-DBS and 400-TBS produced greater LTP and concurrent LTD than 100-TBS in silico for the optimal values of parameters (average results from 3 runs, Fig. 2A) in line with in vivo data (Bowden et al., 2012) which are depicted in Fig. 2B.

The multicompartmental model of granule cell, with realistic active and passive properties, was able to reproduce different experimental results arising from the various experimental protocols (for details see Jedlicka, Benuskova, & Abraham, 2015). The main findings of our modeling study were:

(a) Combined STDP and BCM rules can reproduce the LTP and heterosynaptic LTD, (b) as long as spontaneous activity continues in the input pathways. (c) The degree of LTD depends on the degree of LTP, due to the implemented homeostatic BCM rule that stabilizes cell firing rate. (d) Standard 100 Hz-TBS gives counter-intuitively poor LTP and LTD because this protocol is very good at firing granule cells, which in turn causes the potentiation amplitude parameter to transiently decline, hence braking LTP.

(b) To model denervated-induced dendritic plasticity, we combined morphological and compartmental modeling. By combining full 3D-reconstructions (Vuksic et al., 2011) with published values of passive membrane and cytoplasmic parameters (Schmidt-Hieber et al., 2007), we obtained compartmental models for control (healthy) and denervated dentate gyrus granule cells (Figure 3A). Interestingly, the efficacy of action potential backpropagation was higher in denervated than in control granule cells (Figure 3B). Most strikingly, significant increase in maximum backpropagating action potential (bAP) amplitudes was observed selectively in the denervated dendritic layer (Figure 3B). This result suggests that lesion-induced changes in dendritic morphology facilitate the invasion of bAPs selectively into the deafferented dendritic region.

Fig. 3A shows representative examples for 3-D reconstructions of control (black) and denervated (red) GFP-positive granule cells (Vuksic et al., 2011). Dendrograms of each tree are shown to the right. In Fig. 3B simulated action potential backpropagation (bAP) is plotted for control (black) and denervated (red) granule cells (n = 15, each) as a function of depth in the molecular layer. The border between inner and denervated outer molecular layer is indicated by a dashed line. The IML/OML layer boundary was obtained from the reconstructed cell data.

To predict the consequences of dendritic atrophy (retraction) for the granule cell input-output function we added to the passive model active channels for generating realistic spiking (Schmidt-Hieber and Bischofberger, 2010). As predicted by the higher input resistances in compartmental models of denervated granule cells, the somatic f-I curves were shifted, rendering the neurons more excitable (Fig. 3C, D). The mean output frequencies in somatic f-I curves were strongly increased in denervated cells as compared to control cells. However, when we distributed synapses in dendrites at the same density for compartmental models of both denervated and control cells, we observed similar firing rates (Fig. 3E, F). Thus, in synaptic f-I curves, the greater excitability effectively compensated for the smaller actual number of synapses in the shorter dendrites. Importantly, such remarkable homeostatic compensation for the lower number of synaptic inputs was already present in the passive model, leading to similar somatic voltage output in

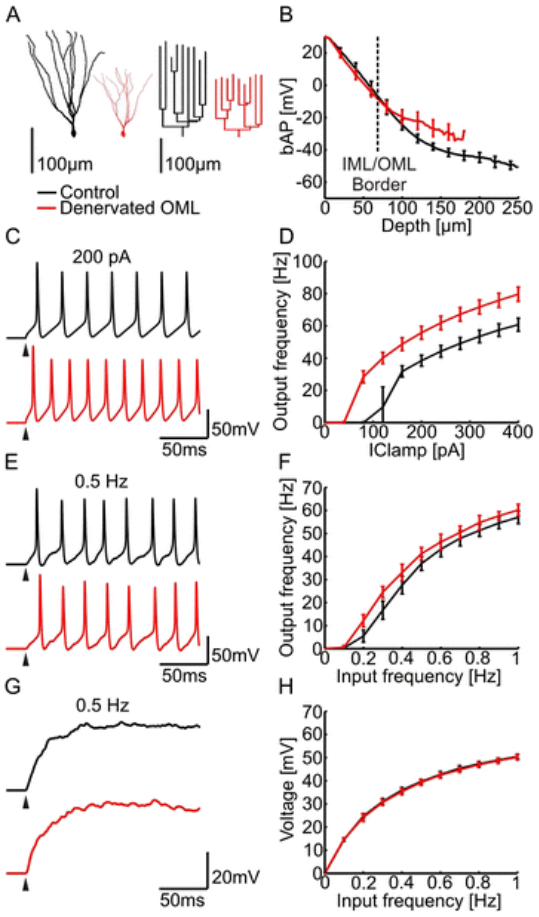

Fig. 3: Action potential backpropagation and excitability in compartmental models of denervated granule cell dendrites (Platschek et al., 2016).

control and denervated cells when all dendritic synapses, distributed again at the same density, were activated (Figure 3G, H). Viewed together,these simulations demonstrate that dendritic remodeling following entorhinal denervation enhances the firing ability of dentate gyrus granule cells and contributes to a homeostatic regulation of their synaptically driven output.

Exploring dendritic reorganization in a variety of morphological models, we found that both phenomena (boost of bAPs and homeostatic enhancement of excitability) that we described for the dentate gyrus granule cell are applicable to any synthetic dendritic tree that we generated. E.g. the homeostatic regulation of excitability was also explained using a simple morphological model: We increased the length of synthetic dendrites grown in a square area by increasing the complexity (Figure 4A). The input conductance increased linearly with the length of dendrite (Figure 4B). Since the average diameter was the same in all cases and the input conductance increases with membrane surface this is not surprising. Because the synapse density does not change, the number of synapses also grows linearly with the length of dendrite. These two measures cancel each other to

reveal an almost constant somatic membrane potential deflection when all synapses are stochastically activated at the same rates (Figure 4C). For the granule cell synthetic and reconstructed morphologies used in our study the linear relation between total dendrite length and input conductance was true (Figure 4D and F), which led to an excitability of the cells that was independent of total length (Fig. 4E and G).

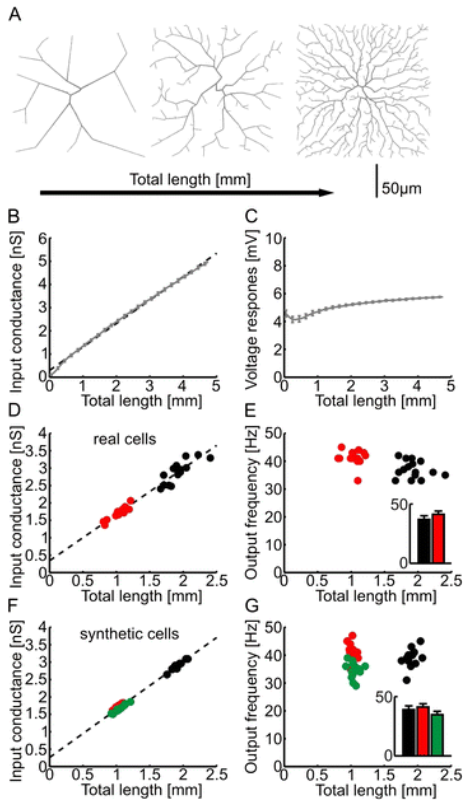

Fig. 4: Morphological models reveal the general electrotonic principle leading to the homeostatic regulation of excitability (Platschek et al., 2016).

3 Discussion

We have found that combining STDP and BCM-like rules with spontaneous activity can replicate the outcomes of three separate in vivo experiments in a biologically realistic granule cell model. The vast majority of computational studies that model synaptic plasticity neglect the fact that in vivo neurons exhibit an ongoing spontaneous spiking which affects the dynamics of synaptic changes. We have studied how key components of learning mechanisms in the brain, namely spike timing-dependent plasticity and metaplasticity, interact with spontaneous activity in the input pathways of the neuron. Using biologically realistic simulations we have shown that ongoing background activity is a key determinant of the degree of long-term potentiation and long-term depression of synaptic transmission between nerve cells in the hippocampus of freely moving animals. This work helps better understand the computational rules which drive synaptic plasticity in vivo. The ongoing spontaneous input activity can explain why the heterosynaptic LTD is routinely seen in the dentate gyrus in vivo, when the hippocampal circuitry is intact while absent in the dentate gyrus in vitro, when the input is severed.

Metaplasticity is defined as the activity dependent and persistent change in neuronal state that shapes the direction, duration and/or magnitude of future synaptic change (Abraham, 2008). A typical computational implementation of synaptic metaplasticity theory is the BCM-like model of synaptic plasticity in which the sign and magnitude of plasticity, as well as the position of the sliding modification threshold, are governed by the level of postsynaptic activity averaged over some past. The BCM-like sliding modification threshold serves a homeostatic function by producing cell-wide changes that keep synaptic plasticity within a working dynamic range and flexible. This has the net effect of keeping both LTP and LTD readily available to respond to future changes in correlated presynaptic and postsynaptic activity. In our model, we implemented BCM-like metaplasticity, in which the metaplastic state affects all synapses across the cell. A critical parameter of the model that affects BCM calculations is the length of the cell-firing integration period. Our model was the most stable and robust when using a relatively fast integration period of one minute. This result is consistent with recent network modeling studies (Zenke et al., 2013, 2015).

In the study focusing on dendritic plasticity, we used computational models to predict the effects of dendritic plasticity on the electrotonic structure and intrinsic excitability of denervated dentate granule cells. In the specific case of the denervated granule cells, our simulations revealed that these neurons are, as expected, electrotonically more compact than control granule cells. As a consequence, backpropagating action potential (bAP) attenuation was significantly reduced in their denervated dendrites. Notably, this boost of bAPs was restricted to the denervated dendritic layers. Since bAPs that reach back to the synapse are thought to be involved with strengthening synaptic weights (i.e. with synaptic plasticity), this result indicates that dendritic remodeling could contribute to a homeostatic strengthening of surviving synapses on denervated dendritic segments. Moreover, simulations of somatic and dendritic f-I curves revealed an increased excitability of the cells. In conjunction with the smaller number of synapses this led to a homeostatic maintenance of firing rates in denervated granule cells. Thus, the shortening of dendrites helps to restore the normal firing pattern of granule cells and normalizes information throughput to the hippocampus.

Importantly, using generalized morphological models we unraveled the general principles that led to these two homeostatic features of dendritic remodeling:

a) Using a general morphological model, we were able to show that the spatially selective enhancement of action potential backpropagation is not only present in

the specific case of denervated granule cells but, remarkably, in any dendritic morphology. The retraction of a single dendritic branch or a large dendritic region will lead to a tightly focused reduction in the attenuation of bAPs in the targeted area. This mechanism will enable any dendritic tree which undergoes structural remodeling including extension or shortening of its distal branches to adjust local synaptic plasticity specifically in the remodeled dendritic subcompartments.

b) Remarkably, the increase in excitability of granule cells after denervation compensated exactly for the smaller number of excitatory synapses, suggesting that these structural changes of the granule cell dendritic tree return granule cell excitability to a physiological working level. In other words, by remodeling the size of its dendritic tree a denervated neuron can exquisitely calibrate its excitability and adapt it to the available afferent input. Such a mechanism counteracts the denervation effects and appears to be a homeostatic mechanism by which neurons regulate their activity under injury conditions. Similarly to the bAP enhancement, using a general morphological model, we have shown that this homeostatic mechanism is not only present in granule cells but represents a fundamental feature of all dendritic trees which undergo lengthening or shortening of their branches while keeping synaptic density constant. A change in input conductance gets canceled out by a change in the number of synapses leading to firing rate independent of the length of dendrites.

Collectively, our data imply that denervation-induced structural adaptations of neurons counteract the loss of synaptic inputs due to denervation and thus contribute to neuronal homeostasis. In contrast to the current view, which regards denervation-induced dendritic retraction as detrimental for a neuron, we have proposed that this form of dendritic remodeling returns a denervated neuron to its functional state and may, in fact, be restorative.

(1) & (2): Synaptic plasticity is dependent on postsynaptic depolarization, which may arise from activation of synapses but may also be enhanced by bAPs. Since dendritic plasticity affects both action potential backpropagation as well as neuronal excitability, it can potentially influence synaptic plasticity. However, the link between synaptic and dendritic plasticity has not yet been explored. Therefore, future experimental and computational studied could provide new insights into the interaction between these two important forms of neuronal plasticity.

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