Review of the DSc thesis of Karri Lamsa

The thesis is based on 5 papers published and reviewed in high-impact journals. Karri Lamsa, using technically tedious methods (perforated patch recording followed by re-patching of the neuron to label it for classification) convincingly proved that:

-Inhibitory neurons in the hippocampus and the neocortex exhibit various forms of activity-induced, learning-related long-term plasticity.

-The actual form of plasticity is interneuron type specific and has been proven to be different from the classical NMDA receptor mediated LTP of the excitatory-to excitatory connections in terms of its induction mechanisms and expression (e.g. mediated via Ca permeable AMPA receptors, induction might need anti-Hebbian pairing).

-The finding has been corroborated by in vivo experiments as well as in human in vitro slice preparations.

-Interneuron plasticity strongly modifies the local neuronal network behavior and permanently changes signal transmission through polysynaptic circuits.

The results presented are novel, the Candidate established that inhibitory cell plasticity is a general phenomenon. The works had been peer reviewed in international scientific journals and were found to be original and high quality.

During his scientific carrier Karri Lamsa supervised 4 PhD students, participated as a tutor in doctoral programs and trained 6 postdoctoral fellows. Organized several domestic and international symposia. He is also a member of a large body of scientific committees and won several prestigious grants.

The presentation of the Thesis is rather succinct, but the attached original papers contain all important details. Still, since a DSc Thesis is considered as a kind of summary of a part of a carrier I am missing a concluding synthetizing discussion with an outlook.

My questions are the following:

When exploring a question that needs fine control of parameters the details, like perforated patch to avoid dialysis of intracellular millieau, are important. Several homeostatic mechanisms have been demonstrated that fine tune cellular and network parameters, so that the network activity converges to a stable level. Therefore, parameters in a silent slice drift from normal values. The ACSF in the rodent experiments contained 2.5K 2.5Ca 1.3Mg, that results in a relatively low background activity level. Also, a cut was made between the CA3 and CA1 further decreasing network activity. The consensus nowadays is that a more excitable ACSF ~3.5K 1Ca 1Mg better approaches in vivo composition and will result in higher (more in vivo like) firing rates and spike distributons. To what extent can the fact that the measurements were made in silent slices can influence the observed mechanisms?

Also, 100uM picrotoxin was used in the experiments. Why was it used? It switches off inhibitory feedback and influences network dynamics (activity level). Since the demonstrated plastic processes are

sensitive to the activity level and the correlations, this intervention influences network behavior. Could the effects be demonstrated without blocking inhibition? Why was a different (3.5K, 1Ca, 3Mg) ACSF used in the human case? In some sense it is more excitable: higher K and lower Ca, though the high Mg blocks NMDA receptors and thus probably decreases excitability.

The most difficult part for me to untangle was to understand the similarities and differences of the plastic processes in the different cases. First, it is difficult to compare the different cases, since different recording configuration were used, and the details given were not of similar depth. Second, it is important to distinguish the location of the plastic changes as well as the induction requirements. Plasticity can happen through changes of synaptic transmission or changes in the integrative properties of a neuron (change in resting potential, input resistance or firing threshold). The plasticity can also be homosynaptic, i.e. input specific, or heterosynaptic, affecting the function of the non-driven input too. It also can be Hebbian, that requires tight temporal correlation or (as shown by the candidate) anti-Hebbian. Therefore, it is crucial to define all details of the examined plasticity process with experiments addressing the conditions, time scale and mechanism of the plastic process in question. For example the classical NMDA mediated excitatory to excitatory plasticity that is present in the connections of most principal neurons (evidently with the exception of the mossy fiber input to granule cells) is: homosynaptic and therefore input and pathway dependent, it is highly sensitive to the temporal correlation of the activation of the pre and postsynaptic elements (STDP, Hebbian) , as well as it lasts for hours to days (some experimental approach allow this conclusion). In the case of the presented papers it was not evident for all experiments whether the plasticity revealed was homo- or heterosynaptic and to what extent were precise temporal correlation needed. For example, in the 2007b paper the pathway specificity of the effect had been checked, while in other cases not. I miss a summary figure that collects and details the similarities and differences of the observed plasticity cases (question marks are valid elements). I also miss a synthesis in the conclusion chapter. An outlook to the literature (modeling can be useful here) would be useful in finding a function to these different forms of plasticity? How do they contribute to the stabilization of network dynamics and learning?

Minor comments:

“at both the PV+ basket cells as well as the ivy cells could generate either LTP or LTD in these conditions.” They hypothesized brain state dependence, i.e. depending on the actual processing mode of the network, the same input or correlation might cause plasticity of different directions. This might argue somewhat against long-term plasticity. Brain states change on the scale of seconds, so this type of plasticity must be rather a short- or medium term one.

p10 top: “Compound EPSCs in were confirmed by observing less than 100 pA increases in the evoked EPSC amplitude when gradually increasing stimulation intensity.” It is difficult to understand the sentence.

p19, 2nd para: “we found that the fast-spiking CA1 interneurons can *generate* either LTP or LTD following high-frequency glutamatergic fiber activity.” Consider replacing the verb (*demonstrate, undergo)*!

Fig6: a schematic drawing of the experimental arrangement would be helpful

Based on the publication and his contribution to science I deem the application sufficient for Open Debate and to serve as a basis for the Degree of Doctor of the Academy of Sciences.

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