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Hippocampal long-term potentiation (LTP) – past, present and future

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Dear readers,
Some of the most interesting questions of our time are how we learn and how our brain stores information. In 1949 Hebb postulated that synaptic strength, which reflects the transmission of information between neurons, increases during learning and memory as a consequence of coincident pre- and postsynaptic activity. However, experimental evidence that brain synapses are plastic had to wait until the discovery of long-term potentiation (LTP) by Bliss and Lømo (Oslo and London, 1966, 1973). They observed, that high-frequency stimulation (so-called tetanization) of excitatory synapses in the hippocampal formation produced a rapid and long-lasting increase in the strength of these synapses. Meanwhile multiple forms of LTP, and its physiological counterpart long-term depression (LTD), have been found at many synapses throughout the brain and described in well over ten thousand papers.

After more than 50 years of LTP research this experimental model has come of age but remains the most popular approach for studying cellular mechanisms of learning and memory. Since the early days of its discovery, the question has been raised as to whether LTP is a simple model or indeed a mechanism for memory storage. It should be admitted that studies of LTP and of memory are based on different levels of analysis. LTP is a property of a selected single synapse or synapse population, which serves to adjust synaptic efficacy, whereas memory formation is a specific network operation, which enables the adaptation of an individual organism to one or the other change in its environment. Today we know that besides many types of learning, also many types of LTP exist – in different brain regions as well as at one and the same synapse. LTP and LTD are increasingly considered as an important component of learning-related changes in neuronal networks.

Originally, most experimental studies were performed in the rodent archicortex (mostly dentate gyrus *in vivo* and hippocampal area CA1 brain slices). These two regions of the hippocampal formation have been the most widely studied because they allow easy access to field potential recordings of a population of many cells in a simple cortex as a precondition to unveil the function of the hippocampus in the formation of episodic and spatial memory. The two main measures in extracellular LTP studies are the so-called field excitatory postsynaptic potential (fEPSP) of glutamatergic synapses and the population spike, the latter reflecting the number and firing synchrony of action potentials elicited by a bunch of 50-100 CA1 pyramidal and dentate granule cells, respectively.

In this special issue we present reviews on the discovery of hippocampal LTP and selected topics of ongoing work. All chapters were selected from former or present research groups of the Leibniz Institute for Neurobiology and the Center of Behavioral and Brain Sciences in Magdeburg (Germany) as well as their international partners. In the eighties of last century, a pioneering group was set up in Magdeburg in the former German Democratic Republic, led by Hansjürgen Matthies (1925 – 2008). The Magdeburg group began to investigate whether LTP expression was associated in any way with various learning tasks. While *in vitro* studies of LTP were usually completed 10-60 min after tetanization at this time, the Magdeburg team was the first to record LTP in acute slices for up to 10 hours after tetanization, enabling thereby the discovery of the distinguished properties of late LTP. The instability of the more precise intracellular or clamp recordings does still not allow the investigation of synaptic plasticity beyond 1-2 hours.

This special issue starts with a review on hippocampal LTP by some of the pioneers in the field (Bliss et al.). Therein the original discovery and the properties of classic LTP are described. Also, the role of N-Methyl-D-aspartate receptors (NMDARs), dopamine receptors and the dependence of LTP on protein synthesis are explained. Moreover, an interesting new aspect of synaptic plasticity is discussed – the heterogeneity of plastic mechanisms at synapses within a single pathway. Bliss et al. argue that depending on input parameters very different and partially overlapping mechanisms can lead to LTP.

The article by Manahan-Vaughan focuses on metabotropic glutamate receptors (mGluR) which are directly linked to intracellular signalling cascades. These receptors not only contribute to the stability of hippocampal encoding and the longevity of synaptic plasticity, they can also support synaptic information storage independent of NMDA receptor activation and are important for the acquisition and retention of long-term memory.

Mikhaylova and Kreutz suggest in their article that stability and plasticity of dendritic spines seems to be compartmentalized in clusters. They propose that functional clusters, rather than single synaptic contacts, may be a fundamental unit for the storage of long-term memory. In such a scenario, the required strength for potentiation can be reduced when a nearby spine becomes potentiated. The authors discuss several molecular mechanisms for the crosstalk with neighbouring spines which allow long-term memory storage.

Growing evidence points to a key role of impaired synaptic plasticity in various forms of brain pathology, such as the functional disintegration of synapses during early Alzheimer's disease (AD), which manifests as mild cognitive impairment in human patients. Balschun and Rowan describe how the progression of specific components of AD pathology in animal models as amyloid β and the tau protein modifies LTP and LTD, thereby allowing the sensitive recognition of early synaptic dysfunction, a better understanding of dementia mechanisms, and the use of LTP / LTD paradigms to find new lead compounds for AD therapy.

Spike timing-dependent plasticity (STDP) is an interesting approach to study synaptic plasticity at single cell level. This model is slightly different from classic LTP and focusses on the interaction of only 2 neurons where a presynaptic and a postsynaptic spike are elicited in a limited time window of several milliseconds. Here Edelmann and Lessmann demonstrate the important role of neuromodulatory transmitters in the extracellular space (dopamine, acetylcholine, noradrenaline) as well as the synaptic release of intercellular mediators (BDNF, endocannabinoids) for STDP.

This special issue cannot consider all important cornerstones in LTP-research from the last half-century. Homeostatic plasticity and LTP of other brain structures were not included here. For going deeper into selected fields, I recommend additional reviews mentioned in the single chapters of this issue.

With the advancement of new imaging and genetic engineering technologies, the field will in future certainly focus more on the study of synaptic plasticity in large networks during memory formation (in other words on the interaction of plastic synapses from different brain structures). The complexity of genes and epigenetic changes involved in LTP is still not clear. Not very much is known on the role of microglia, the resident immune cells of the brain, in synaptic plasticity.

I hope that the articles of this special issue will update the neuroscience community on some of the latest insights into LTP as an excellent model for understanding some fundamentals of memory storage in the nervous system. I am grateful to the editorial board of Neuroforum for choosing our fascinating topic and thank all contributing authors for their dedicated efforts.

With best wishes,
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