Theta burst like stimulations lead to formation of BDNF dependent memory traces

Creating and storing memory traces in our brains is essential for learning, logical thinking, creativity, and for being able to recall persons, events, and facts throughout life. Memory traces are created by joint electrical activity in nerve cells (neurons) that are interconnected by “plugs” that are called synapses, and that allow to transfer electrical activity from a sending (presynaptic) to a receiving (postsynaptic) neuron. During learning, neurons that are co-active build new synapses among each other, thereby facilitating joint activity in the future. This wiring of synaptic connections is called synaptic plasticity. It requires the activity-dependent release of signaling molecules (e.g. proteins) from pre- or postsynaptic neurons that turn on synaptic growth processes that initiate synaptic plasticity. Ultimately, these growth processes lead to a long-lasting (for years or even decades) increase in the number of synapses between certain sets of neurons, whose co-activity codes for a specific memory.

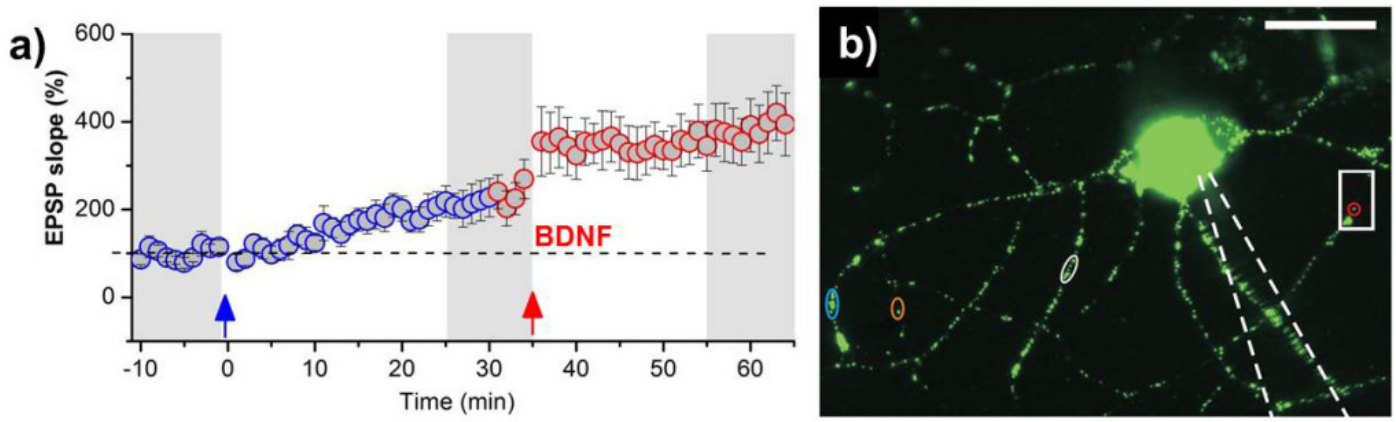

Fig. 1. a) Recording of synaptic strength (i.e. “EPSP slope”) vs. time induced by a single shock STDP protocol (blue) and a theta burst STDP pattern (red), respectively. Both types of synaptic plasticity coexist and can be induced subsequently in the same pair of synaptically connected neurons in the hippocampus. Both STDP stimulation protocols lead to different types of synaptic strengthening (LTP) in hippocampal neurons. However, theta burst STDP leads to secretion of BDNF that generates LTP, whereas the single shock LTP occurs independent of BDNF release and action. b) Hippocampal neuron containing fluorescently labelled BDNF (green) in the processes of the postsynaptic cell. Colored regions of interest show BDNF containing vesicles which are secreted by theta burst STDP stimulation.

To understand the cellular processes underlying learning and memory formation, scientists record electrical activity of synaptically connected neurons in acutely isolated brain slices of selected brain

regions, including the hippocampus. The hippocampus is part of the so-called limbic system, which is central for memory storage processes and is dysfunctional in neurodegenerative diseases. Long-lasting changes in synaptic activity between connected neurons are termed long-term potentiation (LTP), which represents an accepted cellular model of learning and memory formation. An important key player in this process is the protein brain-derived neurotrophic factor (BDNF) which is released from neurons following intense electrical activity. While BDNF mediates cellular growth processes during development, later, it is crucially involved in information storage at synapses. Understanding the cellular mechanisms of information storage in the brain is essential for the development of efficient therapies against highly prevalent neurodegenerative disorders such as Alzheimer's disease and other types of dementia. Since the level of endogenous (i.e., in the body produced) BDNF is dramatically decreased in demented patients understanding the function of BDNF in memory processes seems of utmost importance to counteract these diseases.

In this study we used special "spike timing-dependent plasticity" (STDP) protocols to establish LTP in acute hippocampal brain slices. These STDP protocols of electrical activity resemble activity patterns that can be recorded in the hippocampus "in-vivo" (i.e., in living animals) during learning. Depending on the exact rhythm of STDP stimulation distinct molecular processes are recruited to build up the memory trace. Typical patterns of hippocampal brain activity, which can also be observed in-vivo, consist of so-called theta rhythms with short bursts of high frequency activity. Other STDP protocols use repeated single shocks of activity to induce synaptic plasticity. Using either the single shock or the theta burst STDP protocols we can induce two different forms of LTP in synaptically connected hippocampal neurons. Our data show, that the theta burst like stimulation protocol relies on activity-dependent secretion of endogenous BDNF from postsynaptic neurons. The released BDNF then enables long-lasting strengthening of synaptic transmission between the synaptically connected neurons. Further, our experiments show that the secreted BDNF protein binds to specific targets, called TrkB receptors, on the postsynaptic neuron to mediate the synaptic plasticity process.

Taken together we show that theta burst rhythmic activity of neurons which can also be observed in the hippocampus during learning in vivo leads to secretion of endogenous BDNF that drives the establishment of long-lasting memory traces. These results could be important for efficient BDNF related treatment strategies for neurodegenerative disorders such as Alzheimer's disease.

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