Thrita. 2015 December; 4(4): e30569. DOI: 10.5812/thrita.30569

Published online 2015 November 1. **Review Article**

Synaptic Neuronal Plasticity

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Received: June 15, 2015; **Accepted:** June 16, 2015

Context: The current study aimed to review research articles concerning cortical representational plasticity following the manipulations of inputs.

Evidence Acquisition: This review article compromised previous studies in PubMed, Google Scholar and Scientific Information databases according to the keywords since 1988.

Results: CA1 neurons depolarization paired with CA3 presynaptic input result in EPSPs amplitude enhancement called LTP. Theta-burst stimulation of layer IV produced long term potentiation (LTP) in the granular primary motor cortex, but the agranular or primary somatosensory cortex was capable of generating LTP in case of GABAA receptor inhibition. Upper layers (UL)-induced, and White Matter WM-induced plasticity in layer VI corticogeniculate neurons were produced through type-5 metabotropic glutamate and N-methyl-D-aspartate (NMDA) receptors, respectively. Calcineurin and cannabinoid type 1 receptors are involved in WM-induced and UL-induced het-LTD, respectively. Long-term potentiation of inhibitory postsynaptic currents (IPSCs) was produced in FS-GABA neurons in layer II/III of the mouse visual cortex by tetanic activation.

Conclusions: In summary, the current study presents rational evidences for specific fundamental forms of plasticity, containing associative long-term potentiation and depression of excitatory and inhibitory postsynaptic potentials.

Keywords: Neuronal Plasticity; Cortex; Hippocampus

1. Context

Neuroplasticity or brain plasticity, is the process in which brain's neural synapses and pathways are continually modified due to environmental, behavioral, thinking, emotions and neural changes as one learns and memorizes new data during brain development. Sometimes, synaptic pruning occurs within the changes that brain deletes the neural connections that are no longer necessary or useful and strengthens the necessary ones.

In general, this experience-dependent reorganization of the synaptic networks is a way for brain to fine-tune itself for efficiency. This reorganization can induce both anatomical (brain activity due to a given function can move to a different location) and physiological alterations.

Scientists have taken many important steps to recognize the molecular mechanisms of these elementary plasticity processes and define the learning underpinnings that direct their induction.

It is a challenging task to prove that synaptic plasticity is necessary and adequate for developmental dynamic cortical rearrangements.

2. Evidence Acquisition

Hebbian plasticity introduces synaptic strength increment between neurons. In somatosensory cortex, sensory inputs that fire nearer in time have more probability to demonstrate neighboring points on the peripheral sensory sheets (1). This kind of plasticity in adult animals is thought to have a fundamental effect on both reorganization and development of cortex. Since it is based on the temporal correlations of inputs and since inputs from neighboring skin areas should in general be more correlated than nonadjacent areas, neighboring cortical areas should represent neighboring surface areas, thus establishing a topographic map (1).

Associative or Hebbian synaptic plasticity is thought to be based on the developmental changes in receptive fields of neurons caused by experience and applied for many computational models of cortical plasticity. In some areas and cortical lamina, including somatosensory (2, 3), auditory and visual cortex (4) can be induced by pairing protocols. Learning and memory underlie the variation of synaptic efficacy between two neurons.

Spike timing dependent plasticity (STDP) is a temporally dissymmetric form of Hebbian learning elicited by temporal associations between the action potentials of pre- and post-synaptic neurons. Previous studies show some factors affecting STDP, containing dendritic location, the nonlinear integration of synaptic moderation through complex spike trains and inhibitory and neuromodulatory inputs.

The important characteristics of Long Term Potentiation/Long Term Depression (LTP/LTD) which make it a molecular mechanism for Hebbian neuroplasticity are: (a) Rapid production: LTP/LTD can be rapidly produced by tetanic stimuli; (b) Input specificity: LTP/LTD induction occurs only at stimulated inputs; (c) Associativity: Weak inputs can produce LTP/ LTD in the presence of strong inputs depending on precise timing (spike-timing dependency); (d) Cooperativity: Multiple weak inputs can summate in space or time to produce LTP/LTD; and (e) Long-lasting: The effects are immediate and last several hours. These features of LTP/LTD direct neural networks based on Hebbian principles, and also manage a benchmark to assess other models of neuroplasticity.

3. Results

3.1. Information Flow Through the Neocortex

Sensory information terminate primarily in L-IV and also lower in L-VI and L-III (5) via the thalamocortical axons. The shortest latency to sensory stimuli is detected in L-IV neurons (6, 7). The information primarily flows through L-IV to L-II/III to L-V to L-VI (8) or L-IV to L-II/III/V to L-VI (6). Outside of the L-IV, receptive fields are larger and responses become more complex. Categorization of the layers according to size of receptive field of somatosensory cortex in rat and monkey and visual cortex in cat, is: L-IV (smallest), supragranular layers, L-III and infragranular layers (6). Sometimes L-III and infragranular sizes equal the ones in the supragranular layers (9).

Simple cells are mostly found in L-IV, whereas in supra- and infragranular layers the degree of orientation tuning is sharper than other layars and the number of complex cells is the highest. Therefore, neurons of each level are gathering information from a larger receptive field of neurons in the previous level, diverging out to the next level, and finally form larger and more integrated receptive fields.

3.2. LTP and LTD of excitatory postsynaptic potentials (EPSPs)

3.2.1. LTP of EPSPs

LTP is the long-lasting strengthening of synaptic efficacy after tetanic stimulation of the presynaptic neuron (Bliss et al. 2004). CA1 neurons depolarization paired with CA3 presynaptic input result in EPSPs amplitude enhancement called LTP (10). In fact, the synchronized activity of pre- and post-synaptic neurons results in the potentiation of the synaptic transmission. Therefore, they must have a coincidence detector that exhibits the concurrent activity of pre- and post-synaptic neurons. The N-Methyl-D-aspartate (NMDA) receptor, a ligand-gated calcium channel, acts as a coincidence detector for presynaptic and postsynaptic depolarization (10). The resultant transient rise in intracellular Ca^{2+} concentration activates Ca^{2+}/ calmodulin-dependent protein kinase II and protein kinase C. These enzymes phosphorylate the cAMP-Response-Element-Binding-protein (CREB) which triggers CREB-dependent gene expression (11).

Presynaptic processes mediate LTP, and retrograde messengers such as nitric oxide and endocannabinoids deliver the message to the presynaptic cell to change the neurotransmitter release (12).

Previous studies show that theta-burst stimulation of layer IV produced LTP in the granular primary motor cortex, but the agranular or primary somatosensory cortex was capable of generating LTP in case of GABAA receptor inhibition.

Three protocols induce LTP: (a) pairing, intracellular postsynaptic depolarization is paired with low-frequency stimulation of afferent fibers; (b) Theta-Burst Stimulation (TBS) of afferent pathway, 10 brief bursts at 5 bursts/s, each burst containing 4 pulses at 100 Hz; and (c)tetanus, a 100-Hz, 1-s stimulation of the afferent pathway. Physiological relevance of the mentioned protocols is probably significantly different.

Tetanus-induced (13, 14) and pairing-induced LTP by stimulation of the white matter (WM) (15) can be produced in pyramidal neurons in L-II/III and L-V. Some factors increase the probability of LTP production: GABAergic inhibition blocking, removing Mg 2+, or slices taken from immature animals (13, 14). Totally, inhibition decrement or excitation increment raises the probability of LTP production. Kirkwood et al. (13) could induce LTP in L-II/III by TBS stimulating of L-IV with a success rate of over 80%.

Previous studies demonstrate that LTP in visual cortex mostly happens in synapses of layers II/III, IV, and V (16, 17).

In our previous study we found corticogeniculate (CG) neurons of L-VI in visual cortex that receive top-down synaptic inputs from cortical upper layers (UL), and bottom-up inputs from the white matter (WM), WM-induced and UL-induced plasticity can be induced by NMDA and type-5 metabotropic glutamate receptors, respectively (18).

3.2.2. LTD of EPSPs

In homosynaptic LTD that synaptic activity is necessary to induce synaptic depression, synaptic efficacy reduces following low frequency repetitive stimulation (19). In granular and agranular areas homosynaptic LTD could be produced by low frequency stimulation (1 Hz for 15 minutes) of layer IV.

Heterosynaptic LTD is a passive depression in which activating another pathway induces depression of an inactive pathway(s). LTD is induced by low-frequency protocol in the WM/L-VI to L-IV in younger animals when inhibitory postsynaptic potentials (IPSPs) are blocked (20). Previous studies show that LTD in visual cortex is induced mostly in synapses in layers II/III, IV, and V (17, 18). In the authors previous study, in CG neurons of L-VI, it was found that cannabinoid type 1 receptors and calcineurin under-

lie the UL-induced and WM-induced het-LTD, respectively. Therefore, homosynaptic LTP and heterosynaptic LTD in these cells may change the synaptic transmission efficacy by different underlying mechanisms (18).

In some studies flipping the switch from LTP to LTD depends on some factors:

1. In rat visual cortex slices, LTD was elicited by tetanic stimulation of WM to L-II/III or L-II to L-II/III pathway in the presence of 0.1 - 0.2 M bicuculline (21). In the presence of 0.3 M bicuculline, the same stimulus produced LTP. Therefore, in the presence of low levels of bicuculline, inhibitory inputs will be partially intact, then little postsynaptic depolarization would be elicited.

2. It was thought that LTD and LTP must depend on Ca^{2+} influx. In lower influx of Ca^{2+} below a particular threshold, LTD occurs; but if influx of Ca^{2+} exceeds the threshold, LTP occurs. Results of Ca^{2+} chelators applied to visual cortex neurons is consistent with this matter (22). Another study revealed that the intracellular Ca^{2+} concentration which binds differentially to C and N lobes of the calmodulin kinase, determines that LTP or LTD happens.

3. In associative plasticity, the level of postsynaptic depolarization and LTP or LTD happening depends on the level of the activity of other inputs.

4. Different activation of pre- and post-synaptic neurons can determine the happening of LTP or LTD. In L-V pyramidal cells if a presynaptic Action Potential (AP) precedes a postsynaptic AP by 10 ms, LTP happens, but LTD happens if presynaptic AP follows a postsynaptic AP (23).

3.3. LTP and LTD of IPSPs

Twenty-five percent of neocortical neurons are GABAergic (24), and approximately 20% (25) of all synapses are GABAergic. Inhibitory plasticity may have a critical role in cortical map reorganization (26). Deafferentiation of visual cortex or somatosensory cortex (27) induces GABA markers down-regulation, while chronic stimulation can elicit an up-regulation (28).

In inhibitory to excitatory synapses (GABAergic onto pyramidal neurons) tetanus stimulation of L-IV in the visual cortex of adult rat (29) could induce plasticity in the presence of both NMDA and AMPA receptor blockers. IPSP plasticity, unlike associative EPSP potentiation, was independent of the membrane potential.

In previous study we found that in layer II/III of the mouse visual cortex, tetanic activation of presynaptic FS-GABA neurons produced LTP of uIPSCs, whereas that of presynaptic non-FS-GABA neurons could not induce LTP; indicating that long-term plasticity of inhibitory synapses on FS-GABA neurons has pathway specificity. The authors proposed that P/Q-type channels may involve in LTP induction in inhibitory synapses between FS-GABA neurons (30). In another study, LTP could induce in motor cortical neurons by tetanic stimulation of sensory cortex (31).

Komaki et.al reported that capsaicin-induced C-fiber deafferentation and also peripheral input alteration can result in plasticity of cortex that was postsynaptic in origin (32).

3.4. Critical Period

During a critical period, early in life, thalamocortical synaptic transmission in the primary somatosensory (S1) cortex of rats is modified by sensory inputs. Thalamocortical synaptic responses produce NMDA receptor-dependent LTP and LTD during a developmental period similar to the critical period in vivo. Reduction in the duration of NMDA receptor currents after the critical period may enable neurons to induce LTP and LTD.

In addition, during the critical period many thalamocortical synapses may be functionally silent at resting membrane potentials and just show NMDA receptor currents but no AMPA receptor currents. Silent synapses convert to functional ones during LTP and exhibit rapid appearance of AMPA currents.

In some cases plasticity is age dependent. For example, in one study on cortical slices taken from two-week-old rats, most slices showed a moderate potentiation (20%-30%) by either 5 or 100 Hz stimulation. This stimulation could not induce LTP in cortical slices taken from younger (one week) or older (three weeks) rats. Therefore, during a critical developmental period of rats after birth synaptic efficacy is increased.

3.5. Structural Plasticity

Unmasking of silent synapses (33, 34) and formation of new synapses (35) associated with LTP-induction indicate structural neuroplasticity after neuronal stimulation. Dendritic spines and synaptic buttons are extremely dynamic in animals, and changes are associated with experience (36-38) and associative learning (35) in a number of brain regions.

Neurogenesis is another kind of structural plasticity. It is believed that neurogenesis occurs in the adult hippocampus and the olfactory bulb (39). Some limited evidence show that neurogenesis also occurs in other brain regions (e.g. neocortex, striatum, amygdala) (40, 41) although this remains controversial (42).

4. Conclusions

In adult animals cortical maps are dynamic. Different forms of synaptic cortical plasticity seem to contribute to cortical recognition. However, it is not known that synaptic and cellular plasticity completely account for the experimental data on cortical restructuring. Many subjects including interlaminar differences in plasticity mechanisms, the role of inhibitory plasticity, the role of homo and heterosynaptic plasticity remain to be proved.

Authors' Contributions

Miss. Arami wrote the paper according to her previous articles and Mr. Jamei collaborated in editing.

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