Korean J Physiol Pharmacol
Vol 18: 457−460, December, 2014
http://dx.doi.org/10.4196/kjpp.2014.18.6.457

Long-term Synaptic Plasticity: Circuit Perturbation and Stabilization

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At central synapses, activity-dependent synaptic plasticity has a crucial role in information processing, storage, learning, and memory under both physiological and pathological conditions. One widely accepted model of learning mechanism and information processing in the brain is Hebbian Plasticity: long-term potentiation (LTP) and long-term depression (LTD). LTP and LTD are respectively activity-dependent enhancement and reduction in the efficacy of the synapses, which are rapid and synapse-specific processes. A number of recent studies have a strong focal point on the critical importance of another distinct form of synaptic plasticity, non-Hebbian plasticity. Non-Hebbian plasticity dynamically adjusts synaptic strength to maintain stability. This process may be very slow and occur cell-widely. By putting them all together, this mini review defines an important conceptual difference between Hebbian and non-Hebbian plasticity.

Key Words: Hebbian Plasticity, Long-term depression, Long-term potentiation, Synapse, Synaptic Plasticity

INTRODUCTION

Hebbian plasticity

'The Organization of Behavior', by psychologist Donald O. Hebb, is considered as one of the most important books in the field of neuroscience. In this book, he exhibited a new notion, "Hebbian learning" that the increased efficacy of synaptic connections were caused by growth or metabolic change that would take place at the synapse between neurons. This is often cited as "Neurons that fire together, wire together", commonly referred to as Hebbian plasticity. Hebbian plasticity is defined as synapse-specific modifications in the strength of synaptic transmission (strengthening or weakening). This Hebbian plasticity is considered one of most well known and well studied long-term changes of synaptic plasticity in the nervous system [1]. Most typical examples of Hebbian mechanisms are long-term potentiation (LTP), and long-term depression (LTD). LTP is an activity-dependent increase in synaptic transmission between two neurons. In contrast, LTD is an activity-dependent decrease in synaptic transmission between two neurons. These major forms of Hebbian plasticity include the postsynaptic change of the preexisting surface-expressed glutamate receptors such as N-methyl-D-aspartate (NMDA) or α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptors [1]. Glutamate is the most abundant excitatory neurotransmitter in the nervous system and induces excitatory synaptic transmission through the activation of glutamate receptors. Glutamate receptors are synaptic receptors and consist of ionotropic and metabotropic receptors [2]. Ionotropic glutamate receptors include NMDA, AMPA, and kainate receptors, which are ligand-gated ion channels and induce fast excitatory synaptic transmission. Metabotropic glutamate receptors are divided into Group I, Group II, and Group III. They are G-protein-coupled receptors that participate in the modulation of synaptic transmission, which is able to mediate slow excitatory synaptic transmission. Ionotropic and metabotropic glutamate receptors are localized on postsynaptic area. However, we note that these glutamatergic receptors can also exist in presynaptic terminals as well as in non-neuronal cells [3,4]. These postsynaptic glutamate receptors play an essential role in excitatory synaptic transmission. For this reason, postsynaptic glutamate receptors in synaptic plasticity have been intensively studied for several decades. Investigating the role of long-term changes of glutamate-mediated responses in brain slice reveals essential roles of synaptic plasticity in behavioral tasks such as anxiety, spatial memory including radial arm and Morris water mazes [5,6]. Indeed, recent studies indicate that long-lasting Hebbian plasticity are postulated to play important roles in various central nervous system development and neurological dis-

Received November 4, 2014, Revised November 11, 2014, Accepted November 12, 2014

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ABBREVIATIONS: AMPA, α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF, brain-derived neurotrophic factor; IEG, immediate-early gene; mEPSC, miniature excitatory postsynaptic current; LTD, long-term depression; LTP, long-term potentiation; MAP1B, microtubule-associated protein 1B; mGluRs, metabotropic glutamate receptors; NMDA, N-methyl-D-aspartate; STEP, striatal-enriched protein tyrosine phosphatase; TACE, tumor necrosis factor-α converting enzyme; TTX, tetrodotoxin.

eases such as autism, syndromic mental retardation, dementia, cognitive loss, addiction, anxiety-related disorders, and pain processing [7-11].

Hebbian plasticity occurs most rapidly at synapses stimulated by afferent activity [12-17]. This synapse-specific plasticity has been intensively studied; that is, LTP or LTD occurs only at synapses stimulated but not at adjacent synapses on the same postsynaptic cell, called input specificity. Postsynaptic response is potentiated by intensive and repetitive presynaptic stimulation, such as burst or high frequency stimulation [12]. This is called LTP because it lasts for several hours. In the same hippocampal slices, we can also detect long-term depression of AMPA receptor-mediated responses. Activation of the specific group I mGluR agonist 3, 5-dihydroxyphenylglyine (DHPG) induces LTD at hippocampal CA3-CA1 synapses [13]. LTD is also induced by weak presynaptic stimulation, such as paired-pulse low-frequency stimulation, which is a weaker stimulation compared to strong high-frequency stimulation in LTP. These LTP and LTD, long-term synaptic plasticity, require newly synthesized proteins including Arc/Arg3.1, MAP1B, STEP, as well as AMPA receptor subunits [13,18].

Hebbian plasticity occurs in a rapid and synapse-specific manner

Hebbian types of long-lasting synaptic plasticity require *de novo* protein synthesis. For example, Brain-derived neurotrophic factor-LTP (BDNF-LTP) and NMDA receptor-dependent late-LTP (L-LTP) are both blocked by agents that inhibit translation. Late-phase of NMDA receptor-dependent LTD is also protein synthesis-dependent. Recent studies indicate that *de novo* protein synthesis is also required for LTD induced by group I mGluR activation [13]. Interestingly, compared to NMDA receptor-dependent LTP and LTD, where the requirement for protein synthesis is delayed, mGluR-LTD requires protein synthesis within 5~10 min [13]. This fast regulation of *de novo* protein synthesis is hypothesized to be captured at active synapses, but their identity and mechanisms remain elusive. One mechanism involves activity-regulated cytoskeletal associated protein (Arc/Arg3.1) in mGluR-LTD. The immediate-early gene (IEG) Arc/Arg3.1 is translationally induced within 5 min of mGluR activation, and this response is very rapid and essential for mGluR-dependent LTD [13]. Synapse-specific LTD in the hippocampus, especially mGluR-LTD, can be expressed by other postsynaptic mechanisms including $G_{\alpha q}$-dependent signaling pathways and the tyrosine phosphatase STEP that dephosphoylates GluR2 on Tyr residues. A recent study has shown that matrix metalloproteases (MMPs) is also critical for mGluR-LTD [19]. In response to activation of group I mGluRs, the MMP tumor necrosis factor-α converting enzyme (TACE) triggers AMPA receptor endocytosis, resulting in group I mGluR-LTD. It is notable that MMP TACE is important for synaptogenesis and synaptic depression, which may require mGluR-dependent synaptic plasticity [19]. However, several questions still remain: molecular links between mGluR1/5 and TACE, or TACE-like proteases, and roles of other known TACE substrates including APP and TNFα. Group I mGluRs have been implicated in certain types of synaptic plasticity and behaviors, such as hippocampal LTP, metaplasticity, spatial learning, and drug addiction. Although the precise cellular and synaptic mechanisms of group I mGluRs in Hebbian potentiation have not been reported in detail, it is clear that group I mGluRs in Hebbian potentiation are critical for synaptic learning and memory storage. For example, group I mGluR5 plays an essential role in BDNF- or dopamine D1 receptor-induced potentiation in the striatum and serves as a robust molecular switch to link effects of neuromoulators and growth factors with use-dependent neuronal plasticity [9]. As mentioned above, multiple forms of Hebbian synaptic plasticity are mediated by various molecular mechanisms [8,9,13,19], and likely occur in local protein synthesis-dependent and synapse-specific manner [13,18].

Non-Hebbian plasticity

Hebbian learning mechanisms such as LTP and LTD are important in rewiring neural circuits during development or fluctuations in the external environment. However, Hebbian plasticity may not be sufficient to understand activity and/or experience-dependent changes of neural circuits over a long period of time since LTP and LTD are positive-feedback processes, which leads to the destabilization of network activity. A major question is how neural circuits can stabilize neuronal network activity over a long period of time. There is evidence for another distinct form of synaptic plasticity to keep stable neural circuits over a long period of time in the face of such sustained inhibition or activation of network activity. It is referred to as non-Hebbian form of synaptic plasticity. In contrast to Hebbian plasticity, non-Hebbian plasticity depends primarily on the post-synaptic activation rather than correlation between pre-synaptic input and post-synaptic depolarization. This non-Hebbian plasticity involves synaptic scaling and intrinsic plasticity. Here we will focus on synaptic scaling as a form of homeostatic plasticity that stabilizes synaptic strength. Homeostatic plasticity adjusts a neuron's synaptic strengths up or down to promote stability [20,21]. To maintain stable network activity is a key process for homeostatic plasticity. One proposed mechanism involves an activity-dependent trafficking of AMPA receptors. Homeostatic scaling of post synaptic AMPA receptors is considered as a mechanism to protect against saturation beyond the ability of neurons to encode information [20]. Sustained inhibition or activation of network activity induces homeostatic changes of surface and synaptic AMPA receptors in neurons. For example, chronic blockade of network activity by TTX, Na channel blocker, for 1-2 days resulted in an increase in surface and synaptic AMPA receptors. On the other hand, increases in network activity by chronic bicuculline treatment, $GABA_A$ receptor blocker, decreased the surface and synaptic AMPA receptors [21].

Homeostatic scaling occurs in a slow and cell-wide manner

Chronic TTX-treatment increased surface and synaptic AMPA receptors, while chronic bicuculline-treatment decreased surface and synaptic AMPA receptors. If then, what is the molecular basis of this homeostatic scaling? This review highlights recent study investigating group I mGluR signals as possible molecular mechanisms of homeostatic scaling of postsynaptic AMPA receptor down-regulation [21]. Generally group I mGluRs play an essential role in Hebbian types of plasticity such as mGluR-LTD, spike-timing dependent plasticity, and diverse cellular signaling that drives AMPA receptor trafficking. Canonically, group I

mGluR signaling in neurons includes a broad range of physiological outputs, such as Ca^{2+} release from intracellular stores, Ca^{2+} influx via TRPC channels, modulation of voltage-gated ion channels, biosynthesis of endogenous cannabinoids, regulation of protein synthetic pathways and activation of PI3K/Akt and Erk signaling pathways. It has been shown that many of these outputs in group I mGluR signaling are coupled by Homer proteins and differentially regulated by the IEG, Homer1a [22,23]. Interestingly, group I mGluRs display agonist-independent activation [21,22], which is only blocked by group I mGluR inverse agonists, Bay 36-7620 and 2-methyl-6-(phenylethynyl)-pyridine (MPEP) [21]. This process may occur slowly and widely in cells. These agonist-independent activities of group I mGluRs can down-regulate surface and synaptic AMPA receptors in homeostatic scaling [21]. This process might be one of the possible explanations to understand homeostatic scaling of postsynaptic AMPA receptors over long timescales.

Over the past few decades, many cellular molecules have been studied extensively to discover the link between activity and surface receptor accumulation to increase our understanding of homeostatic plasticity. Another possible mechanism involves the endocytic proteins, Arc/Arg3.1 [22]. Arc/Arg3.1 is a cytosolic protein that is expressed in response to mGluR activation and is also critical for mGluR-LTD in both hippocampus and cerebellum. Studies of Arc provide a model in which homeostatic plasticity as a non-Hebbian plasticity and Hebbian plasticity may show mechanistic similarities [13,21,24]. As described above, group I mGluRs and their signaling pathways play an essential role in both Hebbian and non-Hebbian synaptic plasticity of postsynaptic AMPA receptors. Indeed, group I mGluRs can regulate synaptic strength as in process of mGluR-LTD and homeostatic scaling, but can also prime synapses to augment the subsequent induction and expression of NMDA receptor-dependent LTP. Theses group I mGluR-mediated cellular mechanisms have attracted a great deal of interest in its role in normal brain function, and its implication for neurological diseases.

CONCLUSION

The molecular and cellular mechanisms underlying non-Hebbian plasticity such as homeostatic plasticity remain elusive but seem very similar to Hebbian plasticity. It is now clear that non-Hebbian plasticity likely occurs in a very slow and cell-wide manner, compared to Hebbian synaptic plasticity. Hebbian and non-Hebbian plasticity may occur in the same cell through the same molecular substrates. But these two distinct forms of synaptic plasticity are triggered by different neural activity patterns. Taken together, understanding two distinct forms of synaptic plasticity and conceptual differences between them will provide novel insights into the role of synaptic plasticity that ultimately drive stable network activity, activity-dependent neuronal connections, synapse strengthening, and weakening under physiological and pathological conditions, such as information processing, storage, learning, neurological diseases, cognitive loss, and drug addiction.

ACKNOWLEDGEMENTS

This work was supported by the 2014 scientific promotion program funded by Jeju National University.

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