Chapter 1

Introductory Chapter: Mechanisms and Function of Synaptic Plasticity

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http://dx.doi.org/10.5772/67891

1. Introduction

Many everyday experiences such as reading a book like this one, classroom learning, drug taking, or stressful situations can result in changes of our brain at different levels. These changes can manifest themselves in altering both the structure and function of neural circuits. Neural circuits are built by neurons, which form points of contacts with each other, the synapses [1]. A given neuron can form thousands of synapses on its dendrites, cell body and axon, and through synaptic transmission, communicates information with other neurons in the nervous system. It is at the synapses that changes in brain function occur through modification of synaptic transmission termed synaptic plasticity (reviewed in [2]). Below, a description of synaptic plasticity is provided in terms of its historical context, mechanisms of its different forms, and directions of research on synaptic plasticity.

2. A brief history of synaptic plasticity

The term plasticity has its origin in science more than 100 years ago and has been attributed to the famous Spanish scientist and founder of modern neuroscience Santiago Ramón y Cajal [3, 4]. His idea that the brain can store information by modifying synaptic connections was expressed in 1894 [5], even 3 years before Charles Sherrington introduced the term synapse for connections between neurons [6, 7]. Subsequently, Ramón y Cajal discovered that neurons are unique entities and synapses are the points of communication between them, the neuron doctrine [8]. It was also Ramón y Cajal who insisted that small spiny protrusions of dendrites, dendritic spines, were not an artifact but real and that they have a key role in mediating synaptic connectivity [9].

The idea and concept of synaptic plasticity gained prominence in the late 1940s with pioneering work by the Polish neurophysiologist Konorski [10] and the Canadian psychologist Hebb [11]. Konorski described plasticity as "permanent functional transformations," and Hebb attributed testable physiologic characteristics to synaptic plasticity [6]. Synaptic plasticity

means that the connections between nerve cells in the brain are not static but can undergo changes, they are plastic. Mammalian brains are remarkably plastic, which implies an ability to modify existing neural circuits and to alter future behavior, emotions, and responses to sensory input [12]. Synaptic plasticity refers to activity-dependent changes in the efficacy of synaptic communication and has been proposed to be critically involved in the remarkable capacity of the brain to translate transient experiences into apparently unlimited numbers of memories that can last for many years.

Even though the notion of synaptic plasticity dates back to the end of the nineteenth century, it took almost 80 years before experimental evidence was obtained to demonstrate that synapses are capable of long-lasting changes in synaptic strength [13]. Timothy Bliss and Terry Lomo experimentally induced an increase in the synaptic strength of neurons in the mammalian hippocampus as a result of electrical stimulation. Such an increase in postsynaptic responses is now called long-term potentiation (LTP). Further experimentation by Serena Dudek and Mark Bear [14] revealed the ability of synapses to change in two directions, namely to increase (LTP) or decrease (long-term depression, LTD) in strength, i.e., synapses undergo activity-driven bidirectional modification. Both LTP and LTD have been found in various brain regions, most prominently the hippocampus [2, 15], cerebellum [16], cerebral cortex [17–19], and the amygdala [20–25] where sensory input has been linked to motor output in fear conditioning paradigms.

3. Synaptic and neural plasticity

Principally, synaptic plasticity refers to the strengthening or weakening of synaptic contacts as a result of increasing or decreasing activity levels of the neurons involved in a particular neural circuit. Synaptic plasticity implies direct regulation of pre- and/or postsynaptic neurons through alterations of the synaptic machinery. Examples include changes (a) of the number of neurotransmitter receptors in the postsynaptic membrane, (b) in the quantity of neurotransmitters released from the presynaptic neuron into a synapse, or (c) in receptor sensitivity to the released neurotransmitters [26–29]. Synaptic plasticity has been found at synapses that convey glutamate-mediated excitation and at other synapses that mediate GABAergic inhibition [2, 30]. Synaptic plasticity takes place at different time scales, from tens of milliseconds to life-long changes in synaptic transmission. Therefore, synaptic plasticity can be classified as either short-term or long-term. Short-term synaptic plasticity occurs at time periods from subsecond to minutes whereas long-term synaptic plasticity changes the efficacy of synapses for hours to years and is thought to form lasting memories that are stored in brain circuits.

The terms neuroplasticity, neural plasticity, or brain plasticity are used in a broader context to indicate changes that occur throughout a person's life either at the synapse or whole neurons or even entire brain regions. The basic premise is the same, namely that certain aspects of the brain or brain function can be changed throughout life [31]. This was not always understood to be the case. Previous studies of the brain suggested the existence of a critical period early in life during which the brain is amenable to changes of structure and function (plastic) and would remain unchangeable thereafter (static) (reviewed in [30, 32]). Likewise, synapses were considered as simple relay stations for information transfer from one neuron to another or

from a neuron to a muscle cell. These relay stations were thought to be established during development and to remain in place throughout life with a relatively fixed synaptic strength of the connection. Neuroscience textbooks nowadays appreciate the extreme plasticity of most synapses such that they are able to change their strength as a result of either their own activity or through activity in another pathway [30].

4. Plasticity, memory, and learning

Plasticity is now known to be an intrinsic property of the brain such that it is not limited by its own genome but can adapt to external stressors, physiological alterations, and a person's experiences. Plasticity manifests itself as dynamic shifts in the strength of preexisting connections across distributed neural networks and as modifications of the mapping between behavior and neural activity that take place in response to changes in afferent input or efferent demand [32]. Not only can existing connections undergo rapid changes, the establishment of new connections through dendritic growth and arborization can follow [33–36]. Synaptic and/or neural plasticity is the mechanism for development and learning, but it is also the basis of much brain pathology as seen in various neurological disorders, and maladaptive synaptic plasticity may contribute to neuropsychiatric disorders [2].

While synaptic plasticity is a key concept in itself for brain function and dysfunction, it has become central to our understanding of the mechanisms of learning and memory. Synaptic plasticity is intimately related to learning and memory because memories are thought to be represented by neural networks that are connected at synapses. One critical concept in this regard is the Hebbian theory [11], which proposes an explanation for neuronal adaptation during the learning process and is considered a basic mechanism for synaptic plasticity. Hebb postulated that coincident activity of synaptically connected neurons leads to lasting changes in the efficacy of synaptic transmission. Experimental evidence supports this hypothesis by demonstrating that modifiable synapses exist in brain and form the basis for learning and memory. Under conditions when a presynaptic neuron repeatedly and persistently stimulates a postsynaptic neuron, i.e., when both neurons are active, synaptic connections are modifiable in their efficacy. Hebb's theory has been summarized in a more colloquial way by Siegrid Löwel's phrase: "Cells that fire together, wire together [37]." One important aspect of Hebb's theory relates to the exact timing of activity of the presynaptic neuron in relation to postsynaptic activity. The presynaptic cell needs to generate action potentials just before the postsynaptic cell and not at the same time, a concept known as spike-timing-dependent plasticity [38].

It is now generally accepted that memories are stored as alterations in the strength of synaptic connections between neurons [30]. Alterations in synaptic efficacy have been traced for hours to months, and therefore, LTP is both the most widely studied and the most popular candidate cellular mechanism for storing information in neural circuits over long-time periods. Irrespective of the usefulness of LTP and LTD as examples of long-lasting synaptic plasticity, some authors have cautioned that it is not clear how LTP and LTD relate to memory, i.e., the causal link between LTP and memory has not been demonstrated convincingly (reviewed

in Ref. [30]), especially for hippocampal LTP. Other forms of memory and plasticity have allowed linking cellular events and circuitry to behavior, e.g., classical conditioning in the invertebrate model *Aplysia*, eye-blink conditioning, and amygdala-dependent fear conditioning [30, 39, 40]. Particularly, cerebellar LTD and amygdalar LTP are considered to directly underlie memory-associated behavioral changes [41, 42].

5. Endocannabinoids as mediators of synaptic plasticity

Over the past two decades, a new set of signaling molecules has been implicated in synaptic plasticity, namely, endogenously generated cannabinoids, the endocannabinoids (eCBs) [2, 43–54]. Two endocannabinoids, N-arachidonoylethanol-amide (anandamide, AEA) and 2-arachidonoylglycerol (2-AG) have been found to be the natural agonists of cannabinoid receptors in the brain, CB1R [46]. These signaling molecules are unusual neurotransmitters because they are not stored in synaptic vesicles in synaptic terminals. Instead, endocannabinoids are made on-demand from membrane lipids of activated neurons and are released nonsynaptically. Nevertheless, they have been shown to be involved in synaptic plasticity in many neural systems in both short-term and long-term plasticity, learning and memory such as extinction of aversive memories [52–56]. Endocannabinoids are known to play a role in synapse formation, neurogenesis, and a number of bodily functions such feeding [57, 58], anxiety, pain reception, and recovery after brain injury [59–62]. Endocannabinoids serve as intercellular messengers in the brain [46]. They act in a retrograde fashion at synapses and presynaptically regulate both glutamatergic and GABAergic synapses to alter release-probability in synaptic plasticity. Endocannabinoids mediate short-term synaptic plasticity through a form of neuronal communication known as DSI, Depolarization-induced Suppression of Inhibition (reviewed in [46, 53, 54]). During DSI, when a principal neuron is activated through experimental current injection or activation of metabotropic glutamate or acetylcholine receptors, the inhibitory input onto that principal neuron is transiently reduced or abolished. When a postsynaptic principal neuron experiences a brief increase in intracellular calcium concentration, it synthesizes and releases endocannabinoids that travel to the presynaptic neuron and bind to cannabinoid receptors triggering an intracellular messenger cascade. The result is a transient decline of incoming inhibitory signals in the form of GABA arriving from presynaptic neurons. During DSI, endocannabinoids travel from the postsynaptic cell to the presynaptic GABA-releasing one and through activation of CB1R turn off neurotransmitter release. Endocannabinoids, thereby, act as retrograde-signaling molecules. DSI works as a transient local effect because endocannabinoids are lipids that cannot diffuse widely in the extracellular watery space of neurons. DSI allows neurons to disconnect briefly from other neurons or alter the strength of synapses made onto them through relieve of their inhibition [46]. DSI is a regulatory process allowing neurons to control their own synaptic excitability in an activity-dependent manner. A corresponding form of short-term synaptic plasticity has been described in the cerebellum, DSE, Depolarization-induced Suppression of Excitation, which reduces synaptic excitation by suppressing presynaptic glutamate release [44].

In addition to serving a role in mediating short-term synaptic plasticity, endocannabinoids have been shown to be critical in several forms of long-term synaptic plasticity. In the hippocampus, endocannabinoids evoke long-term depression at inhibitory, but not excitatory, synapses [63]. Endocannabinoid-mediated LTD (eCB-LTD) was described in the cerebellum [64], in the glutamatergic synapses onto medium spiny neurons in the striatum [65, 66] and at synapses between layer V pyramidal neurons in the neocortex [67]. Here, eCB-LTD does not depend on postsynaptic activation of metabotropic glutamate receptors but requires coincident activation of presynaptic ionotropic glutamate (NMDA) receptors. eCB-LTD in both the dorsal and the ventral striatum with the nucleus accumbens requires postsynaptic activation of group I metabotropic glutamate receptors [2, 68–70]. Differences exist regarding a requirement for concomitant presynaptic activity [71], the known involvement of anandamide as the endocannabinoid [72] and the presence of postsynaptic D2 dopamine receptors [73, 74] in the dorsal striatum.

6. Developments and directions of synaptic plasticity research

Synaptic plasticity has become an overriding theme of brain research in order to understand the nervous system in its function and dysfunction. Over the past several decades, researchers have attempted and succeeded in deciphering molecular and cellular synaptic changes that are the basis for behavior and disease [75–77]. However, even though our understanding of synaptic plasticity has grown tremendously, pivotal questions regarding plasticity and its function remain to this day, e.g., how do the different forms of synaptic plasticity compliment or interfere with each other [55, 78].

Technical advances in neuroscience research are also a major catalyst for progress in synaptic plasticity research. Most recently, among these advances are genetic, optical, and optogenetic methods that allow researchers to manipulate single cells or neural circuits with subcellular precision, at microsecond timescales or through longitudinal electrophysiological and optical recordings [79–89]. Novel experimental and conceptual approaches will pave the way to a more complete understanding of the functional consequences of synaptic plasticity and its implication for health and disease.

Acknowledgements

This work was supported in part by grants from the National Science Foundation (NSF IOS-1355034) and the Charles and Mary Latham Trust Fund.

Conflict of interest

The author declares that there is no conflict of interests regarding the publication of this chapter.

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