

Chapter 2

Basic mechanisms of plasticity and learning

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Abstract

The last century was characterized by a significant scientific effort aimed at unveiling the neurobiological basis of learning and memory. Thanks to the characterization of the mechanisms regulating the long-term changes of neuronal synaptic connections, it was possible to understand how specific neural networks shape themselves during the acquisition of memory traces or complex motor tasks. In this chapter, we will summarize the mechanisms underlying the main forms of synaptic plasticity taking advantage of the studies performed in the hippocampus and in the nucleus striatum, key brain structures that play a crucial role in cognition. Moreover, we will discuss how the molecular pathways involved in the induction of physiologic synaptic long-term changes could be disrupted during neurodegenerative and neuroinflammatory disorders, highlighting the translational relevance of this intriguing research field.

INTRODUCTION

Learning resides on the ability of shaping ourselves upon the experiences we have lived. The memory processes fill our everyday life, allowing the possibility to remember the day in which we were happy to have reached a specific goal, as well as the ability to type quickly on a standard computer keyboard. During the last decades, the scientific community has reached significant milestones in understanding the biologic and molecular basis of learning, unveiling potential pathogenetic pathways that could be affected during the development of different neurological disorders. In this chapter, we will summarize the proposed mechanisms by which the experiences can shape our neural network in brain areas considered crucial for learning and memory, such as the hippocampus and the nucleus striatum. Finally, we will discuss how neural plastic abilities could be disrupted during pathologic conditions, taking advantage of the pre-clinic, and clinic studies performed in neurodegenerative and neuroinflammatory disorders of the central nervous system (CNS).

SYNAPTIC AND NEURONAL BASIS OF LEARNING AND MEMORY

At the end of the 19th century, Santiago Ramon y Cajal suggested that a modification of the existing neuronal connections could play a crucial role in the consolidation of a specific memory trace (Ramón y Cajal, 1894). His intuition required decades to be confirmed, but nowadays the long-term changes in synaptic strength are considered the neurophysiologic basis of learning (Fig. 2.1.). Donald Hebb, in his book “The organization of behavior”, refined the Cajal theory postulating a coincidence detection model in which the connection between two neuronal cells is strengthened by the simultaneous activation of both of them (Morris, 1999). The concept that synapses could undergo activity-dependent changes was further investigated by Terje Lomo in 1966, who highlighted a long-lasting increase in synaptic efficacy depending on the repetitive activation of neuronal network (Lomo, 1966). This was probably the beginning of the era of the long-term potentiation

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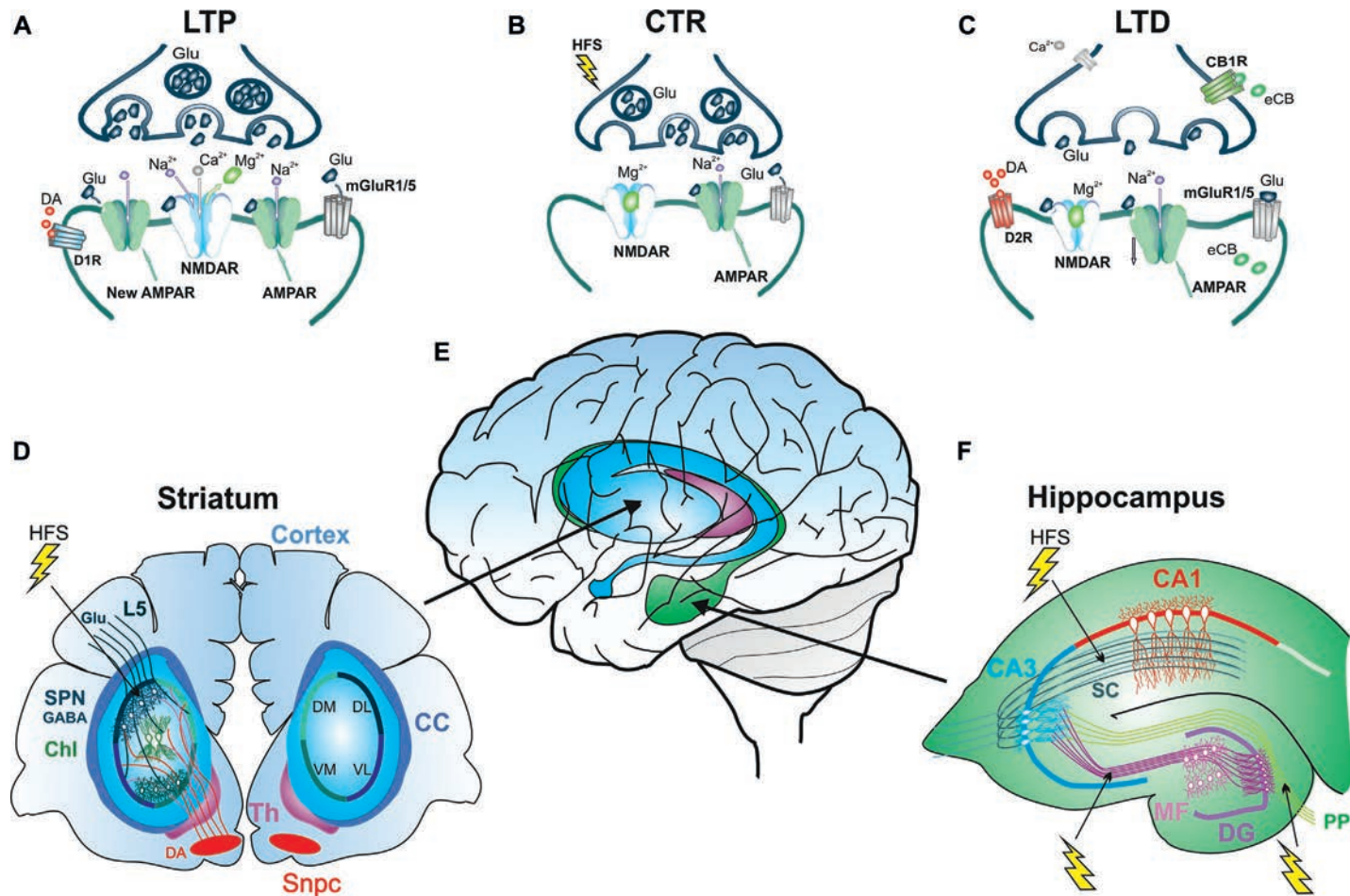


Fig. 2.1. Schematic representation of the mechanisms underlying synaptic plastic changes (*LTD* and *LTP*) at striatal and hippocampal connections. (A–C) Description of the three main forms of synaptic plasticity in a generic synapse. (B) In a control condition before high frequency stimulation (*HFS*), the postsynaptic site contains an *NMDA* receptor closed by the Mg^{2+} blockage and the *AMPA* receptor physiologically open. (A) *LTP* induction after *HFS* protocol induced by the increase of Ca^{2+}/Na^{+} entrance through the *AMPA* receptors and the consequential opening of *NMDA* receptors. (C) *LTD* induction after stimulation protocol in *AMPA*-dependent condition; in this condition, the *NMDA* receptor is closed. (D) Striatal nuclei with the main innervation fibers (see abbreviations below). (E) Representation of striatum and hippocampus localization within the human brain. (F) Hippocampus with the main innervation fibers and the main areas (*CA1*, *CA3*, *DG*) (see abbreviations below). Main Abbreviations: *AMPA*, α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; *CA*, cornu ammonis; Ca^{2+} , calcium; *CC*, corpus callosum; *ChI*, cholinergic interneurons; *DA*, dopamine; *DG*, dentate gyrus; *HFS*, high frequency stimulation; *LFS*, low frequency stimulation; *LTD*, long term depression; *LTP*, long term potentiation; *MF*, mossy fibers; Na^{2+} , sodium; *NMDA*, *N*-methyl-D-aspartate; *PP*, perforant path; *SC*, Schaffer collaterals; *SPN GABA*, gabaergic striatal projection neurons.

(LTP), that was expanded a few years later with the brilliant work of Lomo and Tim Bliss, a psychologist interested in the mechanisms behind memory processes (Nicoll, 2017). In their work, Bliss and Lomo demonstrated that the repetitive activation, named high frequency stimulation (HFS), of the perforant path (PP) fibers projecting to hippocampal dentate gyrus (DG) induced a persistent increase in the amplitude of excitatory post-synaptic potentials (EPSPs) (Fig. 2.1.F) in the same area (Bliss and Lomo, 1973), that could last for several days (Bliss and Gardner-Medwin, 1973). This work is a landmark in the neuroscience field, inspiring the future research efforts aimed at the characterization of the neurobiological basis of learning and memory. Indeed, a few years later, key properties of the LTP were described, such as its “associativity” (a weak input fails to induce LTP on its own but could succeed if tetanized together with a strong input), “cooperativity”, and “input specificity” (a strong input, recruiting numerous synapses can induce LTP but only in the stimulated pathway) (McNaughton et al., 1978; Levy and Steward, 1979). These properties led to consider LTP as a Hebbian phenomenon, requiring the presence of simultaneous post-synaptic cell depolarization and synaptic activation (Kelso et al., 1986; Malinow and Miller, 1986; Wigstrom et al., 1986; Gustafsson et al., 1987). In the same years, the proper characterization of glutamate-based neurotransmission and *N*-methyl-D-aspartate glutamate receptor (NMDAR) properties helped in the understanding of the molecular pathways underlying LTP induction and maintenance (Malenka and Bear, 2004; Bliss and Collingridge, 2013; Nicoll, 2017) (see Fig. 2.1.A and B).

Overall, the discovery and investigation of hippocampal LTP significantly contributed to the understanding of the biological mechanisms through which neural networks can be functionally and structurally shaped in relation to experience (Bliss and Collingridge, 1993). To date, this form of synaptic plasticity has been characterized in several brain areas and represents the best known activity-dependent form of synaptic plasticity (Malenka and Bear, 2004), but other types of synaptic and neuronal plastic changes have been described. Indeed, Ito and colleagues described another form of long-term synaptic change represented by a weakening of the connection at the parallel fiber-Purkinje neuron synapses in the cerebellum (Ito et al., 1982). This form of plasticity was named long-term depression (LTD) and during the last decades it has been extensively characterized in different brain areas, suggesting a cooperation between LTP (Fig. 2.1.A) and LTD (Fig. 2.1.C) in the learning processes (Malenka and Bear, 2004). The property of the synaptic connection to undergo long-term changes seems to fulfill the major requirement for a putative biological basis of learning and memory, allowing a long-lasting

bidirectional modulation of neuronal connections. Moreover, the discovery that it is possible to induce an input-specific and associative LTP at the hippocampal synapses led to the creation of computational hippocampal models underlying the encoding and the retrieval of memory traces (Rebola et al., 2017). It has to be considered that such LTP/LTD-based computational models have been hypothesized not only for the retrieval of the so called “declarative” memory, characterized by a conscious recalling of facts and events previously stored and interconnected, but also for the “non-declarative” memories mainly involved in motor learning and skilled behavior. Indeed, a coordinated potentiation and/or depression of synaptic strength in the basal ganglia network, modulating and filtering the thalamo-cortical connections, has been hypothesized to play a crucial role during the execution and acquisition of a specific motor task (Calabresi et al., 2014).

In the next sections, the main forms of synaptic plasticity will be discussed. However, we need to mention some of the latest findings obtained in the field of neuroplasticity. The development of new techniques, such as optogenetics recordings, has allowed to study the activity and the functional changes of a single neuron during the storage and retrieval of the memory traces. The process of learning has been linked to the formation of a specific neuronal ensemble or memory engram which activation enables the recall of the conditioning event (Tonegawa et al., 2015, 2018; Holtmaat and Caroni, 2016; Titley et al., 2017). In this context, the recruitment of specific neurons seems to rely not only on synaptic long-term changes, but also on neuron-centered plastic mechanisms that enhance or weaken synaptic efficiency and ultimately define the neuron’s contribution in a memory engram (Titley et al., 2017).

Indeed, plastic changes of neuronal intrinsic membrane excitability have been extensively investigated as potential mechanisms of neuronal-based learning processes complementary to synaptic plasticity (Titley et al., 2017). This form of plasticity is thought to involve neuronal voltage- or calcium-dependent ion channels that could modify neuronal membrane excitability, the threshold for the generation of action potential, the spontaneous, and/or evoked spike frequency and the after-hyperpolarization amplitude (Titley et al., 2017). The presence of specific neurons that are more prone or more resistant to be activated in a network could act as a stimulus filter for synaptic connections, integrating the well-known changes in synaptic strength. The presence of neuronal intrinsic plastic changes was found in vivo in the neocortex (Paz et al., 2009; Mahon and Charpier, 2012) and in the cerebellum (Belmeguenai et al., 2010), while its possible contribution to learning processes was suggested by different pharmacologic studies

targeting neuronal channels involved in membrane excitability changes (Tittley et al., 2017).

The possibility that not only synapses, but also neuronal membrane intrinsic properties could contribute to memory processes maintains the study of the neurobiological basis of learning one of the more fascinating field in neuroscience, even after one century from its beginning.

MOLECULAR MECHANISMS OF SYNAPTIC LONG-TERM CHANGES: LESSONS FROM THE HIPPOCAMPUS

NMDAR-dependent LTP

The first molecular insights into the mechanisms of long-term synaptic changes were obtained thanks to the study of hippocampal CA1 area (Fig. 2.1.F), leading to the description of an NMDAR-dependent type of LTP that is considered the prototypic form of synaptic plasticity (Malenka and Bear, 2004). The study of synaptic excitatory transmission led to identify different types of glutamate receptors, such as the NMDAR and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA) (Watkins and Jane, 2006) (Fig. 2.1.B). Both of them are ionotropic receptors, allowing a glutamate-induced entrance of positive ions (such as Na^+ and Ca^{2+}) at the post-synaptic site (excitatory post-synaptic currents, EPSCs) with a subsequent depolarization of the neuronal membrane (Watkins and Jane, 2006). The application of pharmacological antagonists of these receptors highlighted that, while AMPA receptors are required for the basal synaptic transmission (Watkins and Jane, 2006), the blockade of NMDA receptors had no effect on basal EPSCs, but blocked the induction of LTP in the hippocampal area CA1 (Collingridge et al., 1983). Moreover, in the same years, it was shown that the induction of LTP was also blocked by chelating post-synaptic Ca^{2+} , suggesting that the LTP-dependent modifications of the post-synaptic neuron are dependent on the level of free Ca^{2+} (Lynch et al., 1983). The picture became to be more clear after the discovery that NMDAR is characterized by a voltage-dependent Mg^{2+} block, meaning a low current conductance at resting membrane potentials (Mayer et al., 1984; Nowak et al., 1984) which turns into high Ca^{2+} conductance once the cell is depolarized (Macdermott et al., 1986; Ascher and Nowak, 1988) (Fig. 2.1.A). These peculiar characteristics of the NMDAR fit with the hypothesized properties of hippocampal LTP. Indeed, the necessity of a specific stimulation of the NMDAR when the post-synaptic cell is already depolarized reflects the input specificity and the associativity of the LTP.

The mechanisms leading to LTP were expanded and better understood during the successive decades, with

the deciphering of NMDAR-dependent LTP. It is well accepted that the induction of this form of synaptic plasticity is dependent on Ca^{2+} influx through the NMDAR and a rise of its concentration at the post-synaptic site (Malenka and Bear, 2004; Nicoll and Roche, 2013). Nevertheless, it has been long debated which subsequent molecular pathways are triggered by this Ca^{2+} influx, since there may be multiple intracellular cascades triggered by the different induction protocols (Malenka and Bear, 2004). Many different proteins have been suggested to play a role, such as the cAMP-dependent protein kinase (PKA), especially during early post-natal life (Yasuda et al., 2003), the protein kinase C (PKC) and its atypical isozyme protein kinase M zeta (PKM ζ), the mitogen-activated protein kinase cascade (MAPK) and the extracellular signal-regulated kinases (ERKs) (Malenka and Bear, 2004). Overall, the process leading to synaptic LTP seems to involve many different actors, but it is established that the activation of calcium/calmodulin-dependent protein kinase II (CaMKII) is a key event, being both necessary and sufficient for LTP induction (Pettit et al., 1994; Lledo et al., 1995; Giese et al., 1998; Lisman and Raghavachari, 2015).

Specifically, the activation of CaMKII can induce a potentiation of the synaptic transmission, increasing the number of AMPARs expressed at the post-synaptic density (PSD) through activity-dependent exocytosis of intracellular vesicular pools of these receptors and through the lateral diffusion of extra-synaptic receptors into the PSD (Lledo et al., 1995; Choquet and Triller, 2003; Makino and Malinow, 2009; Kennedy and Ehlers, 2011; Patterson and Yasuda, 2011; Opazo et al., 2012; Jurado et al., 2013) (Fig. 2.1.A). The specific mechanisms underlying the recruitment of AMPARs are still under investigation, but it has been hypothesized a role for protein-protein interactions among their cytoplasmic tails or auxiliary subunits (Bredt and Nicoll, 2003; Collingridge et al., 2004; Shepherd and Huganir, 2007; Coombs and Cull-Candy, 2009; Kato et al., 2010), in parallel with the CaMKII-dependent phosphorylation of the subunit GluR1 of the AMPAR (Roche et al., 1996; Barria et al., 1997; Mammen et al., 1997) which could also increase the single channel conductance (Kristensen et al., 2011). Moreover, an interaction between the CaMKII and the GluN2B subunit of the NMDAR seems to be relevant for LTP induction, leading to the recruitment and activation of CaMKII at the PSD (Barria and Malinow, 2005). To complete the picture of NMDAR-dependent LTP, it should be noted that also pre-synaptic changes may contribute to this form of synaptic plasticity, with many possible candidates acting as retrograde messengers (Malenka and Bear, 2004).

After its induction, the subsequent maintenance of LTP requires protein synthesis and gene transcription,

processes involving the recruitment of different signaling molecules such as PKA, MAPK, CaMKII, PKM ζ and the key transcription factor CREB (Abraham and Williams, 2003; Pittenger and Kandel, 2003; Lynch, 2004). LTP-related morphologic changes represent a link between functional and structural potentiation of neuronal connections and these processes include dendritic spine enlargement, new spines growth and the split of enlarged PSDs in two distinct synapses (Yuste and Bonhoeffer, 2001; Abraham and Williams, 2003). Finally, during last years, based on the studies performed in *Aplysia* and *Drosophila*, it has been proposed a role for prion-like synaptic proteins, such as cytoplasmic polyadenylation element-binding protein (CPEB), which could modulate protein synthesis and the subsequent structural synaptic changes underlying the maintenance of long-term memories (Si and Kandel, 2016; Rayman and Kandel, 2017; Asok et al., 2019).

NMDAR-independent LTP

Another prototype of LTP was discovered and characterized in the hippocampus, specifically at the mossy fiber (MF) synapses connecting dentate gyrus (DG) granule cells and CA3 pyramidal neurons (Malenka and Bear, 2004; Nicoll and Schmitz, 2005; Rebola et al., 2017) (Fig. 2.1.F). This form of synaptic plasticity received a lot of attention because it is mechanistically different from the NMDAR-dependent LTP described in the hippocampal CA1 area and similar synaptic plastic changes have been described at corticothalamic and cerebellar synapses (Salin et al., 1996; Linden, 1997; Castro-Alamancos and Calcagno, 1999).

Mossy fiber–CA3 neuron synapses are represented by giant boutons with many release sites expressing different forms of short-term and long-term synaptic plasticity (Nicoll and Schmitz, 2005; Rebola et al., 2017). A peculiar characteristic of these synapses is the presence of a low release probability of neurotransmitter vesicles when the frequency of activation is low (<0.1 Hz), leading to synaptic failures or small amplitude EPSCs (Nicoll and Schmitz, 2005; Rebola et al., 2017). Interestingly, mossy fiber–pyramidal CA3 neuron synapses express marked short-term plasticity when stimulated at higher frequencies, such as paired-pulse facilitation (PPF) and frequency facilitation (FF), which can lead to a significant increase of synaptic strength (Nicoll and Schmitz, 2005; Rebola et al., 2017).

The study of the LTP of these synapses revealed that the involvement of the NMDA receptor is not necessary and it is mainly driven by NMDAR-independent pre-synaptic changes (Henze et al., 2000; Nicoll and Schmitz, 2005). In particular, the induction phase of LTP seems to rely on an activity-dependent increase of

pre-synaptic Ca^{2+} concentration, leading to the activation of Ca^{2+} /calmodulin-sensitive adenylyl cyclase 1 and 8 (AC1 and AC8) and a subsequent increase of pre-synaptic cyclic AMP (cAMP) (Zalutsky and Nicoll, 1990; Castillo et al., 1994; Nicoll and Malenka, 1995; Mellor and Nicoll, 2001; Wang et al., 2003; Nicoll and Schmitz, 2005). The production of cAMP can lead, in turn, to an activation of PKA (Nicoll and Malenka, 1995; Villacres et al., 1998; Wang et al., 2003; Nicoll and Schmitz, 2005) that plays a key role in increasing the release of glutamate from the pre-synaptic sites. The mechanisms through which PKA can mediate this effect are still under investigation, but it has been proposed an involvement of proteins regulating the interaction between neurotransmitter vesicles and the synaptic active zone, such as Rab3A and RIM1 α (Castillo et al., 1997; Castillo et al., 2002). In addition, the activation of pre-synaptic kainate glutamate receptors (Contractor et al., 2001; Lauri et al., 2001, 2003; Schmitz et al., 2003) and a trans-synaptic interaction through the release of B-ephrens (Contractor et al., 2002; Armstrong et al., 2006) could play a modulating role for mossy fiber LTP induction. The mechanisms underlying the long-term maintenance of this form of synaptic plasticity are still unclear and under investigation (Malenka and Bear, 2004; Nicoll and Schmitz, 2005).

Lastly, it was described that mossy fiber–CA3 pyramidal neuron synapses can also express an NMDAR-dependent LTP, requiring the co-activation of NMDAR and metabotropic glutamate receptor 5 (mGluR5), with a post-synaptic calcium rise leading to the activation of PKC (Kwon and Castillo, 2008). The possibility to express different forms of short-term and long-term plastic potentiation could be relevant for the flexibility and the computational role of this crucial area of hippocampal network (Kwon and Castillo, 2008; Rebola et al., 2017).

Main forms of synaptic LTD

In 1992, a protocol named low-frequency (0.5–5 Hz) stimulation (LFS) reliably elicited long-term depression in the CA1 area (Dudek and Bear, 1992) (Fig. 2.1.F), that was dependent on NMDAR and required post-synaptic Ca^{2+} increase and serine-threonine protein phosphatases activation (Dudek and Bear, 1992; Mulkey and Malenka, 1992; Mulkey et al., 1993, 1994). This prototypic form of NMDAR-dependent LTD was also observed in other neocortical areas (Kirkwood et al., 1993; Kirkwood and Bear, 1994) and is now hypothesized to be expressed by all excitatory synapses (Malenka and Bear, 2004).

Similar to LTP, the activation of NMDAR plays a crucial role in the induction of this form of synaptic plasticity. It has been hypothesized that the subunit composition of the NMDA receptor, which could be itself influenced

by the previous synaptic activity, could regulate the propensity of the synapse to express LTP or LTD (Hrabetova et al., 2000; Malenka and Bear, 2004). In the induction process of NMDAR-dependent LTD, a critical role is played by the activation of post-synaptic protein phosphatases, leading to a dephosphorylation of PKA and PKC substrates without affecting CaMKII targets (Hrabetova and Sacktor, 1996; Kameyama et al., 1998; Lee et al., 1998; Van Dam et al., 2002). The expression of LTD could then be allowed by the presence of dephosphorylated AMPARs (Lee et al., 1998), with decreased open channel probability (Banke et al., 2000), as well as by a quantitative reduction of their expression through a clathrin-dependent internalization (Beattie et al., 2000; Lee et al., 2002).

Another type of synaptic LTD was described at the Schaffer collateral (SC)-CA1 pyramidal neuron synapses (Bolshakov and Siegelbaum, 1994; Oliet et al., 1997) and at cerebellar parallel fibers-Purkinje cell synapses (Ito et al., 1982; Ito, 1989), dependent on the activation of group 1 (Gp1) metabotropic glutamate receptors (mGluR) (Aiba et al., 1994; Shigemoto et al., 1994; Huber et al., 2001; Xiao et al., 2001). The expression mechanisms of this mGluR-dependent LTD are thought to involve the internalization of the post-synaptic AMPARs, with some variations among the different brain areas (Malenka and Bear, 2004). For instance, at the mossy fiber synapses it was described an LTD based on the reduction of glutamate release from the pre-synaptic terminal triggered by the mGluR2-dependent inhibition of PKA activity (Yokoi et al., 1996; Tzounopoulos et al., 1998; Nicoll and Schmitz, 2005). After its induction, different mechanisms have been hypothesized to explain the long-term maintenance of the LTD, involving protein synthesis, gene expression and modifications in the regulatory molecular pathways controlling the amount and composition of the glutamate receptors expressed at the post-synaptic membrane (Malenka and Bear, 2004).

The last type of synaptic LTD that we are going to discuss is dependent on the retrograde activity of an endocannabinoid (eCB) messenger synthesized post-synaptically. In the nucleus striatum and other cortical areas, it was described that the activation of post-synaptic Gp1 mGluRs can lead to the production of freely diffusible eCBs, which can activate the CB1 receptors located at the pre-synaptic site, lowering synaptic glutamate release (Sung et al., 2001; Gerdeman et al., 2002; Robbe et al., 2002; Sjostrom et al., 2003) (Fig. 2.1.C). An eCB-dependent LTD was also described in the hippocampal areas (Chevalleyre et al., 2007; Chavez et al., 2010), reinforcing the idea that different molecular pathways can underlie similar long-term synaptic functional changes.

THE NUCLEUS STRIATUM AND THE DOPAMINERGIC REGULATION OF SYNAPTIC PLASTICITY

The basal ganglia network receives afferent connections from many cortical areas and the nucleus striatum exerts a fundamental integrative and computational role in this circuitry, allowing motor learning and skilled behavior (Graybiel et al., 1994). The majority of the striatal neuronal population is represented by GABAergic inhibitory striatal spiny projection neurons (SPNs), which activity is regulated by different types of interneurons, including parvalbumin-containing interneurons, somatostatin-positive interneurons and large cholinergic interneurons (ChI) (Kawaguchi et al., 1995; Tepper and Bolam, 2004) (Fig. 2.1.D). The striatal network is completed by the presence of dopaminergic connections arising from the substantia nigra pars compacta (SNpc), modulating the activity of striatal neurons through different types of receptors, such as D1-like (D1 and D5) and D2-like (D2, D3 and D4) receptors (Aosaki et al., 1994; Calabresi et al., 2007, 2014). A differential/preferential expression of D1-like or D2-like dopamine receptors led to the identification of two main populations of striatal SPNs, traditionally referred as representing, respectively, the direct and indirect striatal pathways (Gerfen et al., 1990; Graybiel et al., 1994). However, the evidence of functional and structural connections between the two pathways challenged this classic and dichotomic view of the striatal network (Calabresi et al., 2014). Interestingly, it was shown that dopaminergic inputs can strongly influence the expression of long-term synaptic changes at the cortico-striatal synapses, with significant implications for pathologic conditions such as Parkinson's disease (PD) (Picconi et al., 2003; Calabresi et al., 2007, 2014).

Specifically, the study of striatal synaptic plasticity started during 1990s, when it was demonstrated that HFS of cortico-striatal fibers was able to induce an LTD at the glutamatergic cortical-SPNs synapses (Calabresi et al., 1992a; Lovinger et al., 1993; Walsh, 1993) (Fig. 2.1.D). This form of synaptic plasticity was not affected by the pharmacologic blockade of NMDARs, but was significantly reduced by mGluRs antagonists (Calabresi et al., 1992a, Lovinger et al., 1993, Walsh, 1993). Moreover, the exposure to D1 and D2 receptor antagonists was able to block the induction of LTD at cortico-striatal SPNs synapses, suggesting a crucial dopamine-mediated regulation of this form of synaptic long-term change (Calabresi et al., 1992a). This hypothesis was further supported by the evidence that LTD in SPNs (i) was absent in rats with a striatal dopaminergic denervation induced by unilateral nigral injection of 6-hydroxydopamine (6-OHDA), a well-known

experimental model of PD, and (ii) was restored in 6-OHDA-lesioned rats by the *in vitro* co-administration of D1 and D2 receptor agonists (Calabresi et al., 1992a).

Further studies suggested that the dopaminergic control of LTD could act through different mechanisms involving other neurotransmitters. In particular, it was proposed that the activation of D2 receptors on striatal cholinergic interneurons may inhibit the release of acetylcholine (ACh) (Wang et al., 2006), inducing, together with D2 receptors activation of SPNs, an increased synthesis and release of eCBs by SPNs ultimately leading to an eCB-dependent LTD (Giuffrida et al., 1999; Gerdeman et al., 2002; Kreitzer and Malenka, 2005; Yin and Lovinger, 2006) (Fig. 2.1.C). Moreover, dopamine can also activate D1 and D5 receptors located on striatal nitric oxide (NO)-producing interneurons leading to an increased synthesis of NO, which seems to strongly influence the induction of LTD via the cyclic GMP (cGMP) pathway (Calabresi et al., 1999; Centonze et al., 2003; Sammut et al., 2006). Taking into account the presence of two different populations of SPNs, it is possible to hypothesize that the induction of LTD at cortico-striatal synapses is modulated in D1 expressing SPNs by the D2 receptor-dependent inhibition of cholinergic interneurons and in neurons expressing D2 receptors by the D1 receptor-dependent NO release (Calabresi et al., 2007) (Fig. 2.1.D).

Concerning the other main type of long-term synaptic plasticity, striatal LTP was revealed by the disinhibition of NMDARs thanks to the exposure of brain slices to a Mg^{2+} -free extracellular solution (Calabresi et al., 1992b) (Fig. 2.1.A). This NMDAR-dependent LTP, similar to LTD, was absent in 6-OHDA-denervated rats (Centonze et al., 1999) and was blocked by the exposure to D1 and D5 dopamine receptor antagonists (Calabresi et al., 2000; Kerr and Wickens, 2001). Conversely, the inactivation of D2 dopamine receptor was able to enhance striatal LTP while its activation was able to block its induction (Calabresi et al., 1997). So, in contrast to what has been described for striatal LTD in which there is a synergistic positive effect of both D1 and D2 receptors, the induction of LTP at cortico-striatal synapses seems to be dependent on the activation of dopamine D1 receptors with an opposite role for D2 receptors. This could rely on the opposite effect that D1 and D2 receptors exert on the cAMP/PKA pathway, respectively activating and inhibiting (Greengard et al., 1999). Indeed, it has been proposed that D1 receptor stimulation could enhance the production of cAMP and the activation of PKA, which can influence the functional state of AMPA and NMDA receptors through different effector proteins such as cAMP-regulated phosphoprotein 32kDa (DARPP-32) (Greengard et al., 1999) (Fig. 2.1.A).

Overall, the dopaminergic projections to the nucleus striatum exert a key role in modulating the synaptic plastic changes occurring at cortico-striatal connections, which could be significantly altered during pathologic conditions such as PD. Some of the clinical features characterizing PD patients could rely on the disruption of the physiologic plastic properties of SPNs, both during the early and the late phases of the disease. We have already mentioned the loss of SPNs LTD and LTP in 6-OHDA-lesioned rats (Calabresi et al., 1992a; Centonze et al., 1999), but an impairment of SPNs synaptic plasticity was also observed in A53T- α -synuclein transgenic mice (Tozzi et al., 2012) and other genetic models of PD (Madeo et al., 2012). Interestingly, a recent study showed with *ex vivo* recordings that, in a viral-vector based model of synucleinopathy resembling early pathologic features of PD, the overexpression of human α -synuclein was able to impair the learning-induced striatal synaptic plasticity with consequent motor learning deficits (Giordano et al., 2018).

Lastly, it was shown that a well-known late complication of PD therapy, levodopa (L-DOPA)-induced dyskinesia, could rely on the existing abnormalities of striatal synaptic plasticity. In particular, the chronic administration of a dopamine repletion therapy was able to restore cortico-striatal LTP in 6-OHDA-lesioned rats, but the animals developing L-DOPA-induced involuntary movements were characterized by a loss of a physiologic striatal synaptic property named “synaptic depotentiation” (Picconi et al., 2003). Synaptic depotentiation is induced by the low-frequency stimulation of a synapse which has previously undergone LTP, allowing the return to a basal pre-LTP synaptic strength. The loss of this form of synaptic plasticity could favor the maintenance of an abnormally potentiated striatal network, ultimately leading to an abnormal motor behavior during chronic treatment with L-DOPA (Picconi et al., 2003).

FROM BENCH TO BEDSIDE: SYNAPTIC PLASTICITY FAILURE IN NEUROLOGIC DISORDERS

Similar to what has been described in PD, a disruption of synaptic plastic properties is thought to play a pathogenic role in different neurodegenerative and neuro-inflammatory disorders. Alzheimer’s disease (AD) can be considered the prototypic neurologic disorder characterized by a disturbance in learning and memory and, indeed, a dysfunction of hippocampal synaptic transmission is considered to occur early during the course of the disease, even before the formation of amyloid plaques and neuronal loss (Selkoe, 2002; Tanzi, 2005). Electrophysiologic studies investigated synaptic plasticity in many experimental models of AD, highlighting a

dysfunction of basal neuronal transmission and of the main forms of synaptic plastic properties (Rowan et al., 2003; Mango et al., 2019). The mechanisms underlying the neuronal and synaptic alterations occurring during AD are still under investigation, but it has been proposed a crucial role for the neurotoxic effects induced by soluble A β -derived diffusible ligands (Lambert et al., 1998), potentially interacting with different molecular targets such as NMDARs, CaMKII and MAPKs (Townsend et al., 2007; Kessels et al., 2013; Pozueta et al., 2013; Mota et al., 2014). In this scenario, the interactions between A β -oligomers and NMDARs seem to be particularly significant. Specifically, exposure to A β -oligomer was able to dysregulate neuronal Ca²⁺ homeostasis (Alberdi et al., 2010), by acting on GluN2B containing NMDARs (Ferreira et al., 2012), and alter synaptic LTP and LTD expression (Lambert et al., 1998; Wang et al., 2002; Shankar et al., 2008; Li et al., 2009; Jo et al., 2011; Mango et al., 2016), potentially through an unbalanced activity of GluN2A and GluN2B NMDAR subunits (Liu et al., 2010; Li et al., 2011). Even if there is still a lot to understand about the involvement of NMDAR in the pathogenesis of the A β -dependent neuronal and synaptic toxicity, its hypothesized central role has led to the clinic use of an uncompetitive open channel blocker of this receptor, memantine, for the treatment of AD patients (Reisberg et al., 2003).

Considering the evidence obtained in a preclinic setting, a great effort was made to investigate the possible alterations of brain plastic properties in patients suffering from AD or mild cognitive impairment (MCI) through non-invasive techniques, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) (Boggio et al., 2011; Freitas et al., 2011; Nardone et al., 2014). Indeed, paired associative stimulation (PAS), characterized by the delivery of an electric stimulus to a peripheral nerve followed by a TMS pulse applied over the primary motor cortex (M1), and cortical responses to rTMS can provide information about LTP- or LTD-like cortical plastic properties (Berardelli et al., 1998; Pascual-Leone et al., 1998; Stefan et al., 2000, 2002; Quartarone et al., 2006; Chen and Udupa, 2009). Thanks to these techniques, different research groups confirmed the hypothesized involvement of cortical LTP- or LTD-like plastic properties in patients suffering from AD since the earliest phases of the disease (Inghilleri et al., 2006; Battaglia et al., 2007; Koch et al., 2011, 2012; Terranova et al., 2013). Of note, the impairment of cortical plastic abilities can be used as a negative prognostic factor since it was found to be associated with a rapid cognitive decline and a progression of the disease (Motta et al., 2018).

Not only neurodegenerative disorders have been linked to a disruption of synaptic plasticity. Indeed,

accumulating evidence points to the presence of a subtle and diffuse synaptopathy during chronic inflammatory diseases of the CNS, such as Multiple Sclerosis (MS) (Mandolesi et al., 2015; Di Filippo et al., 2018). The nervous system has been long considered an immune-privileged site due to the presence of a complex blood-brain barrier, leading to a great underestimation of the crucial role that soluble immune mediators and the resident immune cells play in the modulation of synaptic transmission and plasticity, both during physiologic and pathologic conditions (Di Filippo et al., 2008; Yirmiya and Goshen, 2011; Kettenmann et al., 2013; Wu et al., 2015). Glial and microglial cells are now recognized as active elements of synaptic connections, shaping basal neuronal transmission and synaptic long-term changes (Morris et al., 2013; Wake et al., 2013; Salter and Beggs, 2014). To understand the influence exerted by the neuroinflammatory microenvironment on synaptic plastic properties, different research groups performed electrophysiologic studies in experimental models of MS (Di Filippo et al., 2015; Mancini et al., 2017).

Interestingly, it was shown that the ability of hippocampal synapses to undergo LTP was impaired in the CA1 (Kim et al., 2012; Di Filippo et al., 2013, 2016; Novkovic et al., 2015) or DG areas (Planche et al., 2017) during different phases of experimental MS. The impairment of hippocampal plasticity was also paralleled by behavioral deficits in spatial memory (Kim et al., 2012; Di Filippo et al., 2016). Other works showed a normal LTP induction in the hippocampus but an impairment of synaptic LTD in other brain areas, such as the superior colliculus and the cerebellum (Prochnow et al., 2013), or the presence of an enhanced hippocampal LTP during experimental MS (Nistico et al., 2013). These conflicting results should be interpreted taking into account the differences in the electrophysiologic protocols or in the experimental models which were chosen (Di Filippo et al., 2015). Collectively, the majority of studies pointed to an impaired ability of hippocampal synapses to express normal synaptic plasticity during the neuroinflammatory process, which was found to be associated to classical neuroinflammatory features such as increased levels of pro-inflammatory cytokines (interleukin-1 β , tumor necrosis factor- α , and interleukin-17) (Kim et al., 2012; Di Filippo et al., 2013) and enhanced production of reactive oxygen species (ROS) (Kim et al., 2012). Moreover, the synaptic dysfunction could be strongly influenced by the presence of activated pro-inflammatory microglial cells expressing ROS-producing enzymes (Nistico et al., 2013; Novkovic et al., 2015; Di Filippo et al., 2016), since the inhibition of microglial activation during the course of the disease was able to rescue the observed synaptic and behavioral deficits (Di Filippo et al., 2016). Interestingly, an

inflammatory environment can influence synaptic plastic properties by inducing a modification of the NMDAR subunit composition. Indeed, an increase in hippocampal interleukin-1 β levels was associated with a reduced expression of GluN2B NMDAR subunits during the acute phase of experimental MS (Di Filippo et al., 2013).

The presence of an inflammation-driven synaptic plastic failure was proposed as a crucial contributor to the progression of the neurologic disability in MS patients (Mandolesi et al., 2015), as well as a key pathogenetic factor of the cognitive impairment that could be detected since the earliest phases of MS (Di Filippo et al., 2018). Indeed, an abnormal cortical plasticity was detected in patients with MS by studies performed with rTMS (Stampanoni Bassi et al., 2017). Interestingly, PAS-induced synaptic plasticity was altered during acute MS relapses, supporting the idea that acute inflammation can influence brain plastic properties (Wirsching et al., 2018), and LTP-like cortical properties were found to differ between cognitively impaired and unimpaired patients (Mori et al., 2011), highlighting the potential detrimental cognitive effects of a synaptic plastic failure. Overall, the assessment of brain plastic properties through non-invasive techniques is now considered a potential biomarker for clinical studies examining disease severity, cognitive impairment, motor disability or fatigue during MS (Snow et al., 2019).

CONCLUSIONS

The discovery of the mechanisms underlying the information storage at synaptic and neuronal levels opened new intriguing research directions. We are now facing new questions, trying to understand how synaptic long-term changes could be integrated at the network level in different brain areas during memory and learning processes. More significantly, we are investigating the mechanisms leading to a synaptic plasticity failure during neurologic disorders, in order to identify possible molecular targets suitable for future neuroprotective strategies. The study of the brain plastic abilities using non-invasive techniques confirmed the findings obtained in a pre-clinic setting and suggested new potential non-pharmacologic therapeutic interventions (Koch et al., 2019). Overall, it seems that the long-term research potentiation triggered a century ago is still ongoing.

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