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Multiple forms of long-term synaptic plasticity at hippocampal mossy fiber synapses onto interneurons

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Abstract

The hippocampal mossy fiber (MF) pathway originates from the dentate gyrus granule cells and provides a powerful excitatory synaptic drive to neurons in the dentate gyrus hilus and area CA3. Much of the early work on the MF pathway focused on its electrophysiological properties, and ability to drive CA3 pyramidal cell activity. Over the last ten years, however, a new focus on the synaptic interaction between granule cells with inhibitory interneurons has emerged. These data have revealed an immense heterogeneity of long-term plasticity at MF synapses on various interneuron targets. Interestingly, these studies also indicate that the mechanisms of MF long-term plasticity in some interneuron subtypes may be more similar to pyramidal cells than previously appreciated. In this review, we first define the synapse types at each of the interneuron targets based on the receptors present. We then describe the different forms of long-term plasticity observed, and the mechanisms underlying each form as they are currently understood. Finally we highlight various open questions surrounding MF long-term plasticity in interneurons, focusing specifically on the induction and maintenance of LTP, and what the functional impact of persistent changes in efficacy at MF – interneuron synapses might be on the emergent properties of the inhibitory network dynamics in area CA3.

Keywords

Mossy fibers; CA3; Interneurons; LTP; metabotropic glutamate receptors; bidirectional plasticity

1. Introduction

From the early works by Ramón y Cajal (1893) and Lorente de Nó (1934), it has been acknowledged that differences in anatomical features, including the laminar distribution of dendritic arbors, allow for specialized sources of afferent input and target selection among hippocampal cells. Furthermore, it has become clear that cell distribution and laminar

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organization is associated with specific functions of the hippocampal network (Klausberger and Somogyi, 2008). In area CA3, a prominent region associated with memory function (McNaughton and Morris, 1987, Treves and Rolls, 1992) and several cognitive pathologies (Avoli et al., 2002), inhibitory cells play a pivotal role in controlling the final output of CA3 network activity. Area CA3 contains numerous subtypes of inhibitory interneurons that receive segregated inputs from different sources, including the associational/commissural fibers (A/C) emerged from the axon collaterals of CA3 pyramidal cells, the perforant path (PP), comprised of axons of the layer II stellate cells of entorhinal cortex and the mossy fibers (MF), from axons of the dentate gyrus granule cells. The landmark study by Acsády et al., (1998) showed that the number of MF synapses on interneurons via filopodial extensions, small *en passant* boutons and occasional large boutons surpass those on CA3 pyramidal cells by a ratio of approximately 10 to 1. Interneurons receiving MF input are positioned for feed-forward and feed-back inhibition and can contact hundreds of CA3 pyramidal cells (Lawrence and McBain, 2003). Furthermore, certain interneuron subtypes are entrained by two convergent MF inputs to spatially separated regions of the dendritic tree. This anatomical arrangement could also make these interneurons considerably more responsive to the excitatory drive from dentate granule cells (Cosgrove et al., 2009). The MF preferential innervation of inhibitory cells may underlie the overall suppressive effect of dentate gyrus activation on the CA3 network (Bragin et al., 1997, Penttonen et al., 1997). Indeed, data from *in vivo* experiments indicate that high frequency discharge of single granule cells is able to reliably discharge CA3 interneurons (Henze et al., 2000).

1.1. Anatomical and Physiological Features of the CA3 interneurons

The heterogeneity of interneurons is reflected in their morphological, molecular, and electrophysiological features that mirror the diversity of functions conveyed by these cells throughout the whole hippocampal network. Accordingly, in the last decade attempts have been made to classify hippocampal interneurons by morphology, physiology, receptor expression patterns (Parra et al., 1998), biophysical properties (Chitwood et al., 1999), and molecular expression of markers, such as neuropeptides or calcium-binding proteins (Maccaferri and Lacaille, 2003, Klausberger and Somogyi, 2008). Within area CA1, these collective efforts have resulted in a separation of interneurons into subgroups that have similar actions in the network, providing input to pyramidal cells (or other interneurons) on specific subcellular compartments and acting in discrete time windows (Klausberger and Somogyi, 2008).

In contrast, interneurons in area CA3 have not benefited from these detailed analyses. Although there have been attempts to explain hippocampal events through specific circuit interactions, we still lack the knowledge of how different groups of interneurons in CA3 control network activity, and a detailed analysis of their functions on different brain states has not yet been performed (see Klausberger and Somogyi, 2008). Despite this, it is clear that CA3 interneurons receive significant glutamatergic input (Gulyas et al., 1993, Buhl et al., 1994), and modulate the CA3 pyramidal activity through dendritic shunting and somatic inhibition (McBain and Fisahn, 2001, Romo-Parra et al., 2008). The target cell-dependent nature of excitatory transmission to different interneuron subgroups in area CA3 indicate that CA3 interneurons are not a homogenous group and that they play specific roles in the CA3 network (Toth et al., 2000, Cosgrove et al., 2010).

Using visualized IR-DIC video microscopy and patch clamp electrophysiology combined with biocytin filled pipettes, morphological features of the CA3 interneurons have been described. *Stratum lucidum* (SL) interneurons are recognized for their perpendicular orientation to the *stratum pyramidale* (SP), and are comprised of at least two populations of interneurons, one displaying spines on their dendrites, the other consisting of aspiny interneurons. Each population has bipolar morphology and originates two to five primary

dendrites that show varicose swellings in their course. In some cases, dendrites extend into the *stratum radiatum* (SR) and SP, and occasionally into the *stratum oriens* (SO). Dendrites of SL interneurons do not, however, extend into *stratum lacunosum-moleculare* (SL-M; Gulyas et al., 1992, Soriano and Frotscher, 1993, Spruston et al., 1997).

Ascoli et al., (2009) compared passive and active membrane parameters of interneurons located in the SR and SL-M of area CA3b, reporting no variation between these two groups of cells. Based upon the complexity of dendritic trees, the authors found that CA3b SR and SL-M interneurons can be differentiated into two populations, depending on the number of dendritic bifurcations. This subdivision correlates further with a number of morphometric and physiological parameters, suggesting functional differences between the two groups. In accordance with this, interneurons with higher dendritic branching have faster recurrent collateral synaptic kinetics, larger action potentials and smaller afterhyperpolarizations than interneurons with lower dendritic branching.

Based on electrophysiological properties, Chitwood et al., (1999) found that the membrane time-constant and input resistances of CA3 interneurons are larger than those of interneurons located in the CA1 area (Thurbon et al., 1994). However, the electrophysiological parameters do not differ in the interneurons placed across area CA3, suggesting these neurons may share similar electrotonic properties. This observation was later confirmed for the interneurons somatically located in the SR and the SL-M of area CA3b (Ascoli et al., 2009).

1.2. Synaptic afferents onto CA3 interneurons

Extrinsically, glutamatergic inputs to CA3 interneurons are mainly conveyed by the perforant path and mossy fibers, and intrinsically CA3 interneurons receive a glutamatergic input mediated by the strong recurrent excitation via the extensive network of associational/commissural (A/C) from pyramidal cells. Whereas the PP input is generally restricted to the SL-M of CA3, the MF provides input to interneurons near the hilus via the extensive plexus of fine collaterals, and in area CA3 both from MF traveling ventrally to the SL, and within the SL as the MF bundle proper. Individual MF axons make approximately 150 synapses with cells of the hilus, and these are primarily inhibitory interneurons. MFs innervate CA3 interneurons through the filopodial extensions of the mossy terminals and by small en passant boutons in both the hilar and CA3 regions (Acsady et al., 1998). The dendrites of SR and SL-M interneurons are coextensive with all three of these pathways, extending into the SL-M to encounter the PP, through the SR where the A/C axons travel, crossing the MF within the SL, as well as en route to the SL from the dorsal blade of the DG. Consequently, these interneurons are in position to integrate excitatory input from all three major glutamatergic pathways of the CA3 network.

2. Mossy fiber transmission on CA3 interneurons

2.1. Glutamatergic transmission

Glutamatergic transmission in CA3 interneurons is postsynaptically mediated by three types of ionotropic glutamate receptors, α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), N-methyl-D-aspartate (NMDA), and kainate (KAR) receptors, as well as by different metabotropic glutamate receptors. The MF input has been the most extensively studied, possibly due to the unique anatomical features and functional specializations of the MF associated with their postsynaptic targets. Szabadics and Soltesz (2009), described the functional specificity of the MF input to several subtypes of interneurons somatically located in the SL. Specifically, the MF provides monosynaptic innervation to at least four distinct types of interneurons: fast spiking basket cells, spiny lucidum cells, regular spiking basket cells and ivy cells. Based on the properties of MF innervation, the authors neatly

divide SL interneurons in two groups. One group is formed of fast spiking basket cells and spiny lucidum cells and receives numerous MF inputs with low release probability and small EPSC amplitudes. The second group is comprised of the regular spiking and Ivy cells and receives fewer MF inputs that have high release probability and large EPSCs amplitudes.

2.1.1. AMPAR-mediated transmission—AMPA-mediated transmission is conveyed by synapses formed by calcium permeable and impermeable (CP and CI, respectively) AMPARs. These receptors are composed of several subunits that affect the functional properties of transmission at glutamatergic synapses. CI-AMPA-mediated currents are characterized by an outward rectifying or linear I–V relation, insensitivity to polyamines and are mediated by Na⁺ and K⁺ conductances, with very little Ca²⁺ permeability. CA3 pyramidal cells express predominantly CI-AMPA receptors at MF synapses, which are composed of heteromeric GluR1, GluR2, with lower levels of GluR3 and GluR4. This synapse expresses robust frequency facilitation, short term plasticity, posttetanic potentiation and presynaptic forms of LTD and LTP, mediated by changes in the probability of glutamate release (Schmitz et al., 2001, Isaac et al., 2007).

GluR2-containing CI-AMPA receptors are also expressed in CA3 interneurons, although there is variability in the biophysical and synaptic properties of these synapses. CI-AMPA receptors are present in minor proportion at A/C to SR synapses, where minimal plasticity is observed when high-frequency stimulation (HFS) is applied to CA3 pyramidal cells (Laezza et al., 1999). In the SL-M, however, a greater number of CI-AMPA receptors are expressed, making up around 70% of the AMPARs at MF synapses, which are endowed with mechanisms that support postsynaptic forms of MF LTP (see next section for details). In contrast, SL interneurons express lower levels of GluR2, with subpopulations expressing a significant proportion of GluR2-lacking CP-AMPA receptors at all developmental stages (Dingledine et al., 1999, Toth et al., 2000, Bischofberger and Jonas, 2002; for a review see Isaac et al., 2007).

Native GluR2-lacking CP-AMPA synapses are characterized by enhanced single-channel conductance, fast channel deactivation kinetics (Geiger et al., 1995, Swanson et al., 1997) and an inwardly rectifying current-voltage (I–V) relation. Interneurons expressing CP-AMPA synapses are the main type of AMPA synapse through the SL and SR as well as in basket cells of the DG (Bischofberger and Jonas, 2002). CP-AMPA receptors can be blocked with polyamines like spermine, when they are included in the recording pipette (Toth and McBain, 1998, Laezza et al., 1999) or with philanthotoxin applied externally in the bath solution (Galván et al., 2008, Nissen et al., 2010). This pharmacological sensitivity has emerged as a useful tool to differentiate MF-mediated CP- vs. CI-AMPA transmission in CA3 interneurons. Synaptic properties and plasticity of the interneurons containing CP-AMPA receptors have been extensively studied (for a review see McBain, 2008, McBain and Kauer, 2009). Briefly, the same HFS protocol that triggers MF LTP on CA3 pyramidal cells induces a presynaptic form of LTD on SL interneurons mediated by the activation of mGluR7 and subsequent PKC activity, followed by a downregulation of Ca²⁺ entry in the terminal. The presynaptic expression of mGluR7 has been shown to be a metaplastic switch that mediates the expression of either MF LTD or LTP in response to HFS delivered to MF (Pelkey et al., 2005, Pelkey and McBain, 2008).

2.1.2. NMDAR-mediated transmission—Although MF synapses of area CA3 contain few NMDARs, they are expressed in both pyramidal cells and interneurons. In SL interneurons Lei and McBain (2002), demonstrated that NMDARs are differentially expressed within the CP- and CI-AMPA synapses, with NMDARs at CI-AMPA synapses expressing a lower proportion of NR2B subunits. While large NMDAR-mediated EPSCs are present on CI-AMPA synapses, small and slower NMDAR-mediated responses are associated with CP-AMPA synapses. These authors showed the basic differences in the

properties of the NMDARs expressed in the CI- and CP-AMPA synapses and how they modulate the MF-mediated synaptic transmission. Consistent with these findings, it has been shown more recently that gamma oscillations in area CA3 are increased by the selective activation of NMDARs on SR interneurons resulting from an imbalance between NMDAR-mediated excitation and the tonic inhibition produced by GABA_A receptors (Mann and Mody, 2010).

2.1.3. Kainate-mediated transmission—At the MF to CA3 pyramidal cell synapse, KARs modulate short and long term forms of synaptic plasticity (Schmitz et al., 2001, Contractor et al., 2002). While postsynaptic KARs contribute to excitatory currents (Castillo et al., 1997, Vignes and Collingridge, 1997), presynaptic KAR activity controls the strength of MF transmission (Schmitz et al., 2001, Contractor et al., 2002).

Virtually all CA1 interneurons exhibit functional KAR-mediated responses (Cossart et al., 1998), which provides a strong depolarizing force, enhances synaptic transmission (Cossart et al., 2001, Goldin et al., 2007, Kullmann and Lamsa, 2007), and represents half of the total glutamatergic input of the SO interneurons, a subgroup of inhibitory cells that expresses anti-hebbian LTP (Lamsa et al., 2007). However, even if KARs contribute to the postsynaptic responses in SO interneurons, they do not appear to play a major role in the synaptic excitation of these cells (Oren et al., 2009). Although KARs appear to contribute to excitatory transmission to CA1 SO interneurons, as well as the synaptic plasticity at MF-pyramidal cell synapses, there is some controversy related to the possible mechanisms by which KARs modulate MF transmission (Semyanov and Kullmann, 2001, for a review see Kullmann, 2001), and little is known of their modulatory actions on the CA3 interneurons.

2.1.4. Metabotropic glutamate receptor-mediated transmission—Metabotropic glutamate receptors (mGluRs) modulate synaptic transmission and plasticity of hippocampal interneurons. mGluRs are G-protein coupled receptors and are linked to intracellular second messenger systems. They are characterized based on amino acid sequence and have been divided in three subgroups. Group I, which includes mGluR1 and mGluR5, are expressed postsynaptically in hippocampal interneurons (Baude et al., 1993, Lujan et al., 1996, Ferraguti et al., 2004). Activation of group I mGluRs results in an increase in phospholipase C activity and increased IP₃ production, which in turn mobilizes intracellular Ca²⁺ and calcium induced calcium release. Group II and group III mGluRs are presynaptically expressed in area CA3, and receptors from both groups are present on MF terminals (Shigemoto et al., 1997, Bradley et al., 1999). Both group II and group III mGluRs are negatively coupled to adenylyl cyclase activity and activation of either group can result in a decrease in neurotransmitter release. The MF is characterized by its expression of group II mGluRs on the presynaptic terminal, although the effect of activation is less pronounced at synapses onto interneurons (Toth et al., 2000, Alle et al., 2001, Lawrence et al., 2004, Galvan et al., 2008) when compared to pyramidal cells (Kamiya and Ozawa, 1999). mGluRs have been shown to be important in modulating both short term (Toth and McBain, 1998, Cosgrove et al., 2010) and long term plasticity of MF input to CA3 interneurons (Pelkey et al., 2005, Galvan et al., 2008). Interestingly, the function of different mGluRs at MF synapses onto CA3 interneurons has been shown to be a switch for the polarity of long term plasticity, with mGluR7 dictating the plasticity at MF to CP-AMPA SL synapses, and mGluR1 controlling the bidirectional plasticity of the MF to SL-M synapse.

2.2. GABAergic-mediated transmission

Parallel to the MF-mediated glutamatergic transmission on CA3 cells, strong evidence of GABA release from the terminals of the granular cells of the dentate gyrus has been reported (for a review see Gutierrez, 2005). Indeed, intense MF immunoreactivity for GABA, the

presence of key enzymes required for its synthesis, glutamic acid decarboxylase (GAD)-65 and -67 (Gomez-Lira et al., 2005), the existence of vesicular GABA storage in MF terminals (Zander et al., 2010) and electrophysiological evidence showing the properties of GABAergic transmission in both pyramidal cells and CA3 interneurons has been consistently reported (Safiulina et al., 2006, Romo-Parra et al., 2008). The MF-mediated inhibitory transmission is expressed during early postnatal development and disappears after the third postnatal week in rats, although in guinea pigs the MF GABA response is also expressed in juvenile animals, until the 5th postnatal week (Walker et al., 2001). It is proposed to exert a trophic effect during development and reinforce the hippocampal network (Ben-Ari et al., 1989, Ben-Ari, 2001). The differences in the prevalence of MF GABAergic responses in rats and guinea pigs highlight the marked differences in MF physiology in these two species (Gutierrez, 2002, Safiulina et al., 2006).

In a series of experiments where the MF-evoked glutamatergic transmission was blocked, Walker et al., (2001) found a monosynaptic GABAergic response with the profile of MF-evoked potentials, including facilitation of the synaptic response during repetitive stimulation of the MF and high sensitivity to agonists of group II mGluRs. Fast inhibitory MF-evoked responses have been shown to be mediated by the GABA_A receptors (Walker et al., 2001, Romo-Parra et al., 2008). As might be expected, interneurons in area CA3 also receive this GABAergic input. Safiulina et al., (2006), showed that inhibitory synaptic currents in CA3 SR interneurons also are mediated by GABA_A receptors, exhibit strong paired pulse facilitation when stimulating the granular cells of the DG and are depressed by the activation of group III mGluRs. In the same report, these authors demonstrated that SR interneurons simultaneously co-express GABAergic and AMPAR-mediated glutamatergic responses, supporting the idea that GABA and glutamate can be released independently from the same MF terminal, as previously shown in CA3 pyramidal cells (Walker et al., 2001, Safiulina et al., 2006). It is noteworthy that MF-evoked GABA responses in both pyramidal and inhibitory cells show higher sensitivity with the activation of the presynaptic group III mGluRs by L-AP4, rather than mGluR2 with DCG-IV (Gutierrez, 2002).

MF GABAergic transmission has been suggested to act as a brake to control the excitatory drive in the hippocampus after seizures (Walker et al., 2001). Thus, in CA3 interneurons, the main target of MFs (Acsady et al., 1998), inhibitory MF GABA transmission would contribute to a functional downregulation of the hyperexcitability followed by the prolonged seizures (Sloviter, 1991, Walker et al., 2001). Interestingly, CA3 interneurons of adult rats express a MF-GABAergic response after the induction of seizures (Romo-Parra et al., 2008).

GABAR-mediated responses are known to be modulated by different kinases and phosphatases (Tretter and Moss, 2008), including the cAMP-dependent protein kinase A (PKA) and protein kinase C (PKC), both of which are present in CA3 interneurons (Galvan et al., 2010). In CA3 pyramidal cells the MF GABA_A LTP can be mimicked by the application of the adenylyl cyclase activator, forskolin (Walker et al., 2001) and recently it was shown that postsynaptic activation of cAMP-dependent PKA is required for the paired-induced synaptic potentiation of GABA responses on CA3 pyramidal cells (Sivakumaran et al., 2009). Although PKA and PKC play a critical role in the synaptic plasticity of glutamatergic transmission in SL-M interneurons of the CA3 area, the role of the different kinases in the MF-evoked GABAergic transmission in CA3 interneurons has not yet been explored.

3. Long term plasticity of mossy fiber transmission on CA3 interneurons

MF LTP was one of the first documented NMDAR-independent, presynaptically mediated LTP in the cortex (Harris and Cotman, 1986). The induction of MF LTP, however, remains

controversial because it has been reported as both a presynaptic phenomenon (Staubli et al., 1990, Zalutsky and Nicoll, 1990, Xiang et al., 1994), and also postsynaptically induced (Jaffe and Johnston, 1990, Urban and Barrionuevo, 1996, Yeckel et al., 1999). More recently, however, a postsynaptic form of MF LTP on pyramidal cells of CA3 triggered by the activation of NMDARs, metabotropic receptors and PKC activity has been described (Kwon and Castillo, 2008). Similarly, long term plasticity of the MF input to CA3 interneurons has several forms depending on the cell type and activity state of the network (Figure 1).

3.1. Long term plasticity at MF – SL interneuron synapse

At MF input to interneurons, HFS has been reported to elicit LTD at both CP- and CI-AMPA synapses, though the mechanisms are different depending on the AMPAR subunit composition. When AMPA receptors are GluR 2 containing and thus not calcium permeable, the expression of LTD is postsynaptic and dependent on NMDAR. Following calcium entry into the SL interneuron through NMDAR, AMPARs are internalized via an NSF/AP2 pathway (Lei and McBain, 2004). This phenomenon is very similar to the mechanism underlying LTD at the Schaffer collateral – CA1 pyramidal cell synapse (Luthi et al., 1999, Lee et al., 2002).

At CP-AMPA synapses, where non-GluR2 subunits results in a faster current, the contribution of NMDAR is much smaller, and plasticity at the synapse is NMDAR-independent. Instead, a presynaptic form of LTD is observed that is dependent on the activation of presynaptically expressed mGluR7. When mGluR7, a low affinity group III mGluR is activated, the resultant intracellular signaling cascade activates PKC and inhibits calcium entry through P/Q-type calcium channels that are linked to release at the synapse. Though this is a presynaptically expressed form of LTD, a rise in postsynaptic Ca^{2+} , presumably mediated by the CP-AMPA, is required, which indicates the potential role of a retrograde messenger (Pelkey et al., 2005). LTD can be mimicked at the MF to SL CP-AMPA synapse by prolonged application of the group III mGluR agonist, L-AP4. Interestingly, if HFS is delivered after this chemically-induced LTD, not only is no further LTD observed, but the HFS protocol yields LTP. This LTP occurs only when the mGluR7 has been internalized in response to prolonged (minutes) application of the mGluR7 agonist, L-AP4 (Pelkey et al., 2005) and requires RIM1 α . Thus, at this synapse, the presence of mGluR7 dictates the directionality of long term plasticity, with naïve synapses undergoing LTD.

3.2. Long term plasticity of MF – DG Basket cell synapses

From these early studies of synaptic plasticity at the MF – SL interneuron synapse (Maccaferri et al., 1998) the stereotypical notion arose that HFS of MF would result in LTP at synapses onto pyramidal cells and LTD at “naïve” synapses onto interneurons (Nicoll and Schmitz, 2005, Figure 8). Providing a counter argument to this view was the early observation of LTP at granule cell input to basket cells in the dentate gyrus. In a series of experiments from paired recordings of granule cells and basket cells, it was shown that HFS delivered to the presynaptic granule cell paired with an associative depolarization of the basket cell resulted in a robust post-tetanic potentiation (PTP) followed by a persistent LTP (Alle et al., 2001). HFS of the presynaptic cell while the postsynaptic basket cell was held in voltage-clamp mode to prevent spiking induced LTD. The expression of PTP and LTP is presynaptic but LTP expression requires both a postsynaptic rise in intracellular calcium as well as a presynaptic increase in release probability. Although PKC seems to be involved with both phenomena, MF LTP was only partially attenuated in BAPTA loaded cells, indicating that the induction mechanisms are more resilient to chelation of postsynaptic Ca^{2+} than those underlying LTP induction in SL-M interneurons (see below).

3.3. Long term plasticity of MF – SL-M interneuron synapses

Recently, however, it has been documented that MF input to feed-forward SL-M interneurons undergoes LTP in response to high frequency activity. This LTP is postsynaptically expressed and dependent on mGluR1 α activation, and, in contrast to the CI-AMPA plasticity in SL interneurons is NMDAR-independent (Galvan et al., 2008). The LTP at MF input to CI-AMPA synapses in L-M interneurons can be recapitulated chemically with forskolin application, indicating the involvement of the cAMP/PKA signaling cascade. Furthermore, PKC activation can also mimic the effect of HFS, resulting in a potentiation of the MF-evoked response. Together, the importance of these kinase-mediated signaling cascades to the expression of LTP is an indication that the expression of long term plasticity at glutamatergic synapses onto interneurons may have more overlap with the signaling cascades mediating plasticity in pyramidal cells than previous realized (Huang et al., 1994, Weisskopf et al., 1994, Villacres et al., 1998, Yeckel et al., 1999).

Interestingly, the MF to SL-M synapse provides another example for the potential of bidirectional plasticity. If mGluR1 α activation, or the resulting downstream activation of IP₃R and RyR-mediated CICR from internal stores, is prevented, HFS at the MF to SL-M synapse results in LTD. Both forms of plasticity, however, are postsynaptically mediated and require activation of the L-type voltage-gated calcium channel (Galvan et al., 2008), indicating that SL-M interneurons are equipped with calcium signaling cascades that result in either LTP in naïve synapses, or LTD if the activity-dependent state of the network has prevented mGluR1 α activation.

Additionally, it has been observed in a few CP-AMPA-mediated MF synapses on SL-M interneurons that HFS results in LTD, however this LTD differs from the LTD at CP-AMPA synapses in SL interneurons. Although it is also NMDAR-independent, it can be mimicked by the application of the adenylyl cyclase activator, forskolin (Galvan et al., 2010), which is not true of naïve MF – SL CP-AMPA interneuron synapses (Maccaferri et al., 1998).

3.4. Long term plasticity of MF – SR interneuron synapses

Although somatic position is not accepted as a significant criterion for interneuron classification (Klausberger and Somogyi, 2008), there are considerable differences in LTP/LTD induction mechanisms between CA3 SR and SL-M interneurons. Specifically, changes in synaptic strength in SR interneurons are induced at predominately CP-AMPA synapses, whereas cells expressing mostly CI-AMPA receptors lack use-dependent plasticity (Laezza et al., 1999). Furthermore, despite the indistinguishable quantitative morphological measures of dendrites and axons in interneurons in SR versus SL-M, naïve MF synapses undergo LTD in SR interneurons (Ascoli et al., 2009) and LTP in SL-M interneurons (Galvan et al., 2008).

4. Future directions

The summary provided above highlights the progress that has been made in understanding the complexity of the MF projection system. As we learn more of the details and variety of synaptic mechanisms underlying the long-term plasticity of the MF across its targets, new questions are uncovered. Here we suggest a few future lines of research that are pivotal to the understanding of MF mediated long-term plasticity in interneurons of area CA3.

4.1. The involvement of protein synthesis in MF plasticity in CA3 interneurons

Maintenance of hippocampal LTP requires a series of temporal mechanisms including an early phase of post-translational events followed by transcriptional and translational events

associated with the late maintenance phase of LTP. These phases can be dissociated with inhibitors of protein synthesis (Frey et al., 1988, Frey et al., 1993). For example, both the induction and the early maintenance of MF LTP in pyramidal cells are blocked by protein synthesis inhibitors (Barea-Rodriguez et al., 2000, Calixto et al., 2003). Like MF LTP in pyramidal cells, the induction of MF LTP in SL-M interneurons requires pre- and postsynaptic activity of PKA and PKC; chemical stimulation of PKA or PKC induces a robust enhancement of MF synaptic transmission (Galvan et al., 2010). Whether this form of MF LTP in CA3 interneurons involves protein synthesis or post-translational modifications of proteins associated with the maintenance of LTP remains to be determined. Using cultured hippocampal slices and chemical stimulation of mGluR1 activity, Ran et al., (2009), demonstrated that CA1 Oriens-Alveus interneurons express a form of excitatory LTP which persists for at least 24 hours and requires *de novo* synthesis of proteins immediately after the chemical induction of LTP. By means of genetic manipulation, the authors also found that induction of mGluR1 LTP requires signaling cascades involving Phosphoinositide 3-kinase/mTOR and the MEK/ERK pathway. These data might be relevant to possible MF-mediated signaling cascades involved in the LTP of the CA3 interneurons. Furthermore, cAMP-mediated potentiation of hippocampal transmission has been associated with the activation of genes that lead to the synthesis and distribution of plasticity related proteins (Frey and Morris, 1998). Both these processes -“synaptic tagging” and the recruitment of new sites of synaptic transmission (Bolshakov et al., 1997) - may play roles in the plasticity of MF synapses on CA3 interneurons.

4.2. Spike-timing dependent plasticity on CA3 interneurons

Spike-timing dependent plasticity (STDP; t-LTP/t-LTD) of excitatory transmission on CA3 interneurons also awaits exploration. Different stimulation protocols capable of inducing changes in the synaptic strength of hippocampal interneurons have been useful in unmasking a wide range of biochemical elements underlying synaptic plasticity of the GABAergic cells. From these studies, we have learned that the cellular elements typically associated with STDP are present in the synapses of subpopulations of interneurons in area CA3. These elements include NMDARs (Lei and McBain, 2002, Lei and McBain, 2004), metabotropic glutamate receptors (Galvan et al., 2008), endocannabinoid signaling (Heifets et al., 2008), kinases and activity of neurotrophic factors (Sivakumaran et al., 2009). A systematic exploration of STDP, a Hebbian protocol involving the pairing of a presynaptic action potential with a postsynaptic response where the resulting synaptic strength is determined by the relative timing of activity of the pre- and postsynaptic cells (see Kampa et al., 2007), has yet to be performed in the synapses of inhibitory interneurons where MF LTP or LTD can be induced (Lamsa et al., 2010). For example, a STDP rule instead of a more general Hebbian plasticity rule could result in a faster and more accurate encoding of different memory states by efficiently excluding (via t-LTD) or binding (via t-LTP) MF inputs activated within single gamma cycles. Until such a study is undertaken, the complexity of the inhibitory control exerted by hippocampal interneurons and their role in the functional CA3 network may not be fully appreciated.

4.3. Computational role of MF LTD/LTP in CA3 interneurons

One unique feature of area CA3 is that pyramidal cells are predominantly connected among themselves via the A/C input (Ishizuka et al., 1990), by providing ~7,400 synapses per pyramidal cell (Witter, 2007). It is assumed that this input forms the basis of an autoassociative attractor network, which is capable of storing memory representations via NMDAR-dependent Hebbian LTP. Computational models predict that the combination of low firing probability of dentate gyrus granule cells and sparse MF connectivity in CA3 pyramidal cells is sufficient to produce an efficient pattern separation of incoming neocortical memory representations (O'Reilly and McClelland, 1994, Lisman, 1999, Leutgeb

et al., 2007). It also could be argued that the parallel recruitment of inhibitory interneurons by the MF input could promote a narrow time window for pyramidal cell firing (Pouille and Scanziani, 2001). Therefore, the powerful MF activation of CA3 interneurons could complement the sparse connectivity of the MF input as an additional means for an efficient recruitment of non-overlapping pyramidal cell assemblies. Thus, according to this reasoning it follows that a mixture of target-cell dependent expression of MF LTP/LTD onto CA3 interneurons will significantly affect pattern separation. The development of a theoretical framework in the form of realistic, experimental-data-driven modeling approach may help to elucidate the emergent properties of the inhibitory network dynamics in area CA3 as a result of persistent changes in efficacy at MF–interneuron synapses.

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Figure 1.

The induction of multiple forms of long-term synaptic plasticity at MF synapses on hippocampal interneurons. The induction of MF LTP at dentate gyrus basket cells requires concomitant pre- and postsynaptic activity. Voltage clamp of the postsynaptic cell soma to prevent action potential firing during HFS of the presynaptic cell induces MF LTD. Interneurons somatically located in the Stratum Lacunosum-Moleculare (SL-M) also expresses a Hebbian form of LTP solely at MF synapses containing predominantly CI-AMPA receptors. In the absence of mGluR1 α activation, the same HFS induces MF LTD. On Stratum Radiatum (SR) interneurons MF synapses express LTD. A switch for controlling bidirectional plasticity has not been reported at these synapses. In Stratum Lucidum (SL) interneurons, HFS of MF induces LTD mediated by the presynaptic activation of the mGluR7b, which triggers a postsynaptic mechanism mediated by PKC followed by downregulation of the P/Q calcium channels. In this group of interneurons, HFS triggers MF LTP after internalization of mGluR7 receptor (see text for details). Inset: Anatomical representation of dentate gyrus, CA3 area and the mossy fiber innervated hippocampal interneurons. DG, dentate gyrus; GC, granular cell; MF, mossy fibers. Dotted lines represents the CA3 Stratum Pyramidale.