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REVIEW

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Muscarinic Regulation of Spike Timing Dependent Synaptic Plasticity in the Hippocampus

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Abstract—Long-term changes in synaptic transmission between neurons in the brain are considered the cellular basis of learning and memory. Over the last few decades, many studies have revealed that the precise order and timing of activity between pre- and post-synaptic cells (‘‘spike-timing-dependent plasticity; STDP”) is crucial for the sign and magnitude of long-term changes at many central synapses. Acetylcholine (ACh) via the recruitment of diverse muscarinic receptors is known to influence STDP in a variety of ways, enabling flexibility and adaptability in brain network activity during complex behaviors. In this review, we will summarize and discuss different mechanistic aspects of muscarinic modulation of timing-dependent plasticity at both excitatory and inhibitory synapses in the hippocampus to shape learning and memory.

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Key words: synaptic plasticity, STDP, acetylcholine, muscarinic receptors, pyramidal neurons, interneurons.

INTRODUCTION

Changes in synaptic strength such as long-term potentiation or depression (LTP or LTD, respectively) are thought to be the cellular substrate of the initial stage of learning and memory (Dan and Poo, 2004; Malenka and Bear, 2004; Poolos and Jones, 2004). Cellular mechanisms for plasticity have been proposed to involve functional modification of existing synapses and neurons, as well as physical rewiring of circuits due to synapse formation, elimination and morphological changes, increasing the range of ways by which neurons can modify their synaptic connections (Feldman, 2012). At the functional level, synaptic efficacy is dependent on many factors, including the presynaptic transmitter release machinery, postsynaptic receptors and signal transduction pathways, gene activation and synthesis of new proteins (Malenka and Bear, 2004; Nicoll, 2017). Experimental data and computational models indicate that the precise timing and the temporal order of pre- and postsynaptic action potentials can drive changes in synaptic strength, collectively called spike-timing-dependent plasticity (STDP) (Dan and Poo, 2006; Buchanan and Mellor, 2010; Feldman, 2012). This form of synaptic plasticity is an attractive mechanistic explanation of behavioral learning due to its associative nature. In addition, STDP is sensitive to the actions of numerous neuromodulatory transmitters that signal in the brain during behavior (Sjöström et al., 2003; Seol et al., 2007; He et al., 2015; Cui et al., 2018; Brzosko et al., 2019). Among the different neuromodulatory transmitters, acetylcholine (ACh) is a well-known regulator of cognitive function (Buño and Velluti, 1977; Givens and Olton, 1990; Fuenzalida et al., 2016; Haam and Yakel, 2017), presumably by influencing the function of neurons, including depolarization of the membrane potential (Cole and Nicoll, 1984), modulation of neurotransmitter release (de Sevilla et al., 2002; Drever et al., 2011; Ahumada et al., 2013) and long-term synaptic plasticity (Shinoe et al., 2005; Mitsushima et al., 2013; Morales-Weil et al., 2020). Growing evidence suggests that ACh also shapes timing-dependent synaptic plasticity in the hippocampus to regulate complex behaviors such as learning and memory (Pitler and Alger, 1992; Behrends and ten Bruggencate, 1993; Brzosko et al., 2019). These actions of ACh appear to be mainly mediated by muscarinic receptors (Segal and Auerbach, 1997; Seeger, 2004; Drever et al., 2011; Fernández de Sevilla et al., 2020). In the present review, given the importance of the hippocampus in learning and memory, we discuss works that demonstrate the important role of muscarinic ACh receptors in the control of hippocampal STDP.

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Abbreviations: ACh, acetylcholine; LTD, long-term depression; LTP, long-term potentiation; STDP, spike-timing-dependent plasticity; t-LTD, timing-dependent long-term depression; t-LTP, timing-dependent long-term potentiation.

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SPIKE-TIMING DEPENDENT PLASTICITY

In accordance with the associative nature of synaptic plasticity, Hebb proposed that ''*when an axon of cell A is near enough to excite cell B or repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased*" (Hebb, 1949). Over the last few decades, experimental evidence has shown that the temporal coincidence between the firing of presynaptic action potential and a strong depolarization of the postsynaptic neuron is important for the induction of plasticity at excitatory and inhibitory synapses throughout the brain (Magee and Johnston, 1997; Markram et al., 1997; Bi and Poo, 1998; Debanne et al., 1998). Given its temporal characteristics, this form of associative synaptic plasticity has been called STDP (Abbott and Nelson, 2000; Song et al., 2000; Dan and Poo, 2004, 2006). At many synapses, the canonical STDP is bidirectional and Hebbian in origin, where pre-before-post (pre-post) pairing induces synaptic strengthening known as timing-dependent long-term potentiation (t-LTP), whereas post-before-pre (post-pre) pairing leads to timing-dependent long-term depression (t-LTD). Most forms of STDP are restricted by precise temporal windows (10 to 100 ms time scale) and the temporal rules of STDP vary with brain region, cell, and synapse type (Markram et al., 1997; Bi and Poo, 1998; Fuenzalida et al., 2007; Larsen et al., 2010). Anti-Hebbian forms of STDP where pre-post and post-pre pairing leads to t-LTD and t-LTP, respectively, have also been reported (Wittenberg and Wang, 2006; Lamsa et al., 2007). The multiplicity of timing rules across different neuronal circuits in the brain enables flexibility and synapse-specificity in learning and memory.

Since its discovery, STDP has attracted much interest in experimental and computational neuroscience. It is a favored mechanism for experience- and activity-dependent changes in neural circuits (Abbott and Nelson, 2000; Dan and Poo, 2006; Feldman, 2012; Froemke, 2015) and is observed in diverse neuronal types and in numerous brain regions. In addition to excitatory synapses onto principal neurons, STDP has also been demonstrated at excitatory synapses onto interneurons and at inhibitory synapses onto principal neurons (Tzounopoulos et al., 2004, 2007; Ormond and Woodin, 2009; Ahumada et al., 2013; Huang et al., 2013; Takkala and Woodin, 2013). Moreover, its physiological relevance has been assessed using in vivo recordings in the hippocampus (Fung et al., 2016) as well as at retinotectal (Zhang et al., 1998; Mu and Poo, 2006), somatosensory (Jacob et al., 2007) and corticospinal synapses (Nishimura et al., 2013). Importantly, studies using intact animals provide a direct link between STDP at the synaptic level and altered sensory representations induced in vivo through precisely timed sensory stimuli (Yao and Dan, 2001; Froemke and Dan, 2002; Fu et al., 2002).

Biochemically, t-LTP results when NMDA receptor activation optimally coincides with backpropagation of action potentials (BAPs) to trigger fast and strong intracellular calcium rise in the dendrites of the postsynaptic neuron, whereas t-LTD relies on more moderate calcium changes (Magee and Johnston, 1997; Karmarkar et al., 2002; Sjöström and Nelson, 2002; Rubin et al., 2005) or is triggered when activation of voltage-gated calcium channels precedes that of postsynaptic metabotropic glutamate receptors (mGluRs) to engage retrograde endocannabinoid signaling (Bender et al., 2006; Nevian and Sakmann, 2006). Thus, BAP timing and dendritic excitability play active roles in associative synaptic modifications (Stuart and Sakmann, 1994; Stuart and Spruston, 1998; Paulsen and Sejnowski, 2000) by titrating intracellular calcium. By altering the underlying calcium dynamics, numerous neuromodulatory systems, including cholinergic circuits, are known to modify the induction threshold and the temporal requirements for STDP (Pawlak et al., 2010; Ahumada et al., 2013; Huang et al., 2013; Brzosko et al., 2019). Below, we discuss how ACh influences both pre- and postsynaptic elements via disparate muscarinic receptors to regulate STDP in the hippocampus.

Muscarinic modulation of STDP at excitatory synapses

Cholinergic projections to the hippocampus arise mainly from the medial septum and the diagonal band of Broca complex (Hasselmo, 1999) to activate both muscarinic (mAChRs) and nicotinic (nAChRs) receptors in pyramidal neurons and GABAergic interneurons (Cea del Rio et al., 2010). mAChRs are metabotropic and transduce their signaling through activation of heterotrimeric G proteins, linking ACh activity to a variety of intracellular biochemical signaling cascades (Thiele, 2013). There are five mAChR encoding genes that can be split into two main subgroups: M1, M3 and M5 receptors are all coupled to $G_{q/11}$-proteins and activate phospholipase C, thereby increasing intracellular calcium via IP3 signaling. M2 and M4 receptors are negatively coupled to adenylate cyclase via $G_{i/o}$- proteins (Fig. 1; Wess, 2003), resulting in inhibition of cAMP production and protein kinase A signaling. nAChRs are ionotropic and act by permeating non-selective cations in response to ACh binding to directly depolarize neurons (Dani and Bertrand, 2007). Both mAChRs and nAChRs have been shown to influence synaptic function, with nAChR effects being faster and shorter-lived than mAChRs (Picciotto et al., 2012; Ballinger et al., 2016). Because of the large amount of in vivo and in vitro experimental data demonstrating a key role of ACh and mAChRs in the induction and expression of activity-dependent synaptic plasticity (Segal and Auerbach, 1997; Fuenzalida et al., 2016; Palacios-Filardo and Mellor, 2019; Fernández de Sevilla et al., 2020), we will focus on muscarinic signaling on STDP in this review. For detailed discussions on muscarinic regulation of conventional synaptic plasticity and network dynamics, we refer readers to other excellent reviews (Picciotto et al., 2012; Dannenberg et al., 2017; Fernández de Sevilla et al., 2020).

Activation of mAChRs can either facilitate (Huerta and Lisman, 1995; Shimoshige et al., 1997; Shinoe et al., 2005) or directly induce LTP in the hippocampus

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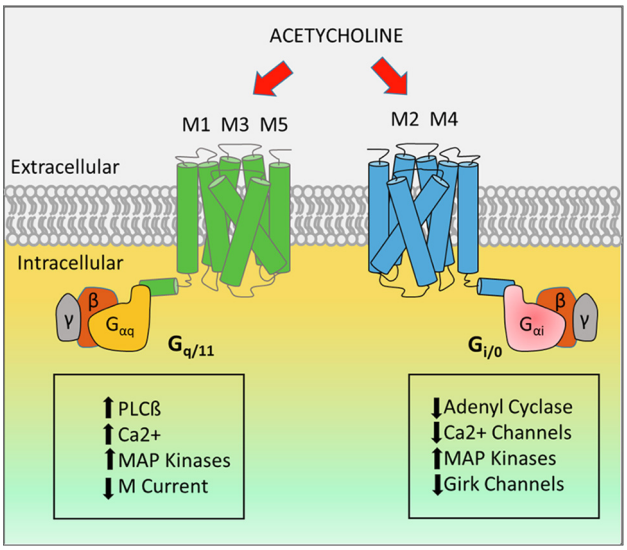

Fig. 1. Subclassification of muscarinic receptor based in G-protein and downstream signaling (modified from Santiago and Abrol, 2019).

(de Sevilla et al., 2008; de Sevilla and Buño, 2010; Dennis et al., 2016). In particular, activation of M1 receptors (M1Rs) are known to trigger an IP3-dependent release of calcium from the endoplasmic reticulum to regulate the induction of conventional frequency-dependent LTP in CA1 pyramidal neurons (de Sevilla et al., 2008; de Sevilla and Buño, 2010; Dennis et al., 2016). Similar modulation of LTP has been reported in the dentate gyrus, where M1Rs regulate the excitability of granule cells by a direct modulation of M-type potassium (K+) and canonical transient receptor potential (TRPC) channels (Carver and Shapiro, 2019). By influencing both excitatory and inhibitory synaptic function and plasticity (de Sevilla and Buno, 2010; Ahumada et al., 2013; Dennis et al., 2016; Fuenzalida et al., 2016), ACh plays an important role in the processing of information needed to regulate several cognitive tasks such as exploration, REM sleep and learning and memory (Dennis et al., 2016; Dannenberg et al., 2017; Niwa et al., 2018). Moreover, cholinergic transmission in vivo has been shown to control the timing and coordination of brain oscillations in the hippocampus (Buzsáki, 2002; Somogyi and Klausberger, 2005). For instance, cholinergic stimulation at the depolarizing peak of the theta cycle is known to facilitate LTP (Huerta and Lisman, 1995). A similar relationship was found for oscillation in the beta-gamma band in the cerebral cortex (Wespatat et al., 2004). Taken together, these findings suggest that brain oscillations provide a region-specific temporal structure of pre- and postsynaptic activity that allows ACh to determine the strengthening or weakening of synaptic contacts.

The role of ACh and specific mAChR subtypes in regulating t-LTP and t-LTD has been less explored. Cholinergic control of timing and coordination of STDP at the synaptic level has been described (Blokland, 1995; Benchenane et al., 2010; Zhao and Tzounopoulos, 2011; Teles-Grilo Ruivo and Mellor, 2013). mAChR activation can induce small changes in the latency of firing of pre- and postsynaptic neurons, altering their relative timing to make the difference between t-LTP or t-LTD induction. At the cellular level, ACh through activation of cholinergic receptors can boost BAPs or reduce spike attenuation during high-frequency bursting (Hoffman and Johnston, 1998; Johnston et al., 1999). By enhancing presynaptic depolarization and BAPs, ACh can profoundly facilitate the induction of STDP and broaden the coincidence window for synaptic modification. Moreover, the temporal window for t-LTP can be narrowed by a reduction of the amplitude and decay time constant of the glutamate-evoked excitatory postsynaptic potential (EPSP). This can be seen during slow afterhyperpolarization (sAHP), when membrane conductance are increased due to the activation of calcium-dependent potassium channels (Fuenzalida et al., 2007). Activation of mAChRs can decrease membrane conductance (Benardo and Prince, 1982; Dasari and Gulledge, 2010; Dasari et al., 2017), consequently reducing sAHP and increasing the amplitude and decay of EPSPs to ultimately facilitate the induction of t-LTP. In addition, mAChR activation promotes action potential backpropagation in CA1 pyramidal dendrites (Tsubokawa and Ross, 1997) and enhances IP3-mediated calcium release provoked by BAPs (Nakamura et al., 2000), which can also lower the threshold of t-LTP induction. Moreover, a STDP protocol applied during a slow muscarinic-induced EPSP enhances t-LTP and prevents t-LTD (Sugisaki et al., 2011). This form of t-LTP is abolished by mAChR antagonists and by prolonged application of the ACh receptor agonist carbachol, likely due to desensitization of postsynaptic mAChRs (Adams et al., 2004).

Muscarinic activation can also suppress t-LTP and favor t-LTD. In CA1 pyramidal dendrites, activation of mAChRs activates an inwardly rectifying potassium conductance, thereby reducing EPSPs and presumably the amount of synaptically evoked intracellular calcium increase (Seeger and Alzheimer, 2001). In addition, bath applied ACh converts a normally Hebbian pre-post pairing protocol into an anti-Hebbian one (Brzosko et al., 2019, 2017). The ability of ACh to turn t-LTP into t-LTD is blocked by mAChR antagonist atropine (Brzosko et al., 2017), suggesting that ACh might facilitate t-LTD by broadening the timing window into the pre-post regime. Given the diverse signaling pathways of different mAChRs, whether muscarinic activation promotes or suppresses synaptic strengthening most likely depends on the receptor subtype recruited and the synapse in question.

The role of specific muscarinic receptors in STDP remains to be clarified. In the stratum radiatum, mAChRs, particularly M1Rs, can augment NMDA receptor-mediated responses (Markram and Segal, 1990; Marino et al., 1998; Zwart et al., 2018). Moreover, activation of M1Rs and M3Rs induces rhythmic bursting of action potentials by regulating potassium channels, such as the small conductance calcium activated potassium channels (SK channels (Robert et al., 2020). Since NMDA-dependent dendritic spikes are suppressed by these potassium channels (Bock and Stuart, 2016), their inhibition by M1Rs (Giessel and Sabatini, 2010; Tigaret et al., 2018) can also boost NMDAR signaling in dendritic

spines. Interestingly, the induction of t-LTP at distal dendrites requires dendritic spikes (Kampa et al., 2007; Buchanan and Mellor, 2010, 2007; Brandalise et al., 2016) that may arise from NMDAR-dependent temporal summation of EPSPs (Wang et al., 2003; Makara and Magee, 2013). Thus, M1R-mediated disinhibition of NMDA receptors would potentiate synaptic potentials and calcium influx in dendrites spine for the induction of t-LTP in hippocampal pyramidal neurons. Indeed, M1R activation has been recently shown to be required for t-LTP induced by place-cell firing patterns during exploration (Tigaret et al., 2018).

The precise role of other muscarinic receptors in the induction and expression of STDP (t-LTP or tLTD) at excitatory synapses within the hippocampus remains to be elucidated. However, their effects on conventional frequency-dependent synaptic plasticity may provide some insights. M2Rs can promote excitatory LTP at the associational/commissural fiber-CA3 synapses, while reduce the magnitude of LTP at mossy fiber-CA3 synapses (Zheng et al., 2012), indicating that synapse-specific rules within the CA3 area of the hippocampus exist for the modulation of mAChR. At Schaffer collateral-CA1 synapses, activation of M2Rs is involved in the enhancement of LTP (Shimoshige et al., 1997). It is thought that activation of presynaptic M2 autoreceptors may restrict cholinergic release and thus differentially engage high affinity receptors like postsynaptic M2Rs and M4Rs (Bujo et al., 1988; Bräuner-Osborne et al., 1996). However, it remains unclear how M2R- and M4R-mediated signaling would lead to LTP. Antagonism of M2/4Rs in vivo, presumably acting to augment ACh release, can induce LTP in CA1 that requires activation of M1/3Rs (Li et al., 2007). Interestingly, activation of presynaptic M3Rs has also been reported to reduce excitatory synaptic transmission (de Vin et al., 2015), complicating the dissection of specific roles of distinct muscarinic receptors.

While excitatory synapses onto principal cells express classical Hebbian forms of t-LTP that are NMDAR-dependent (Caporale and Dan, 2008; Fuenzalida et al., 2010; Feldman, 2012), excitatory t-LTP in hippocampal GABAergic interneurons are NMDAR-independent and requires the activation of calcium permeable AMPARs (CP-AMPARs) in CA1 stratum oriens (Lamsa et al., 2007) and parvalbumin-positive (PV^+) interneurons (Le Roux et al., 2013). This anti-hebbian form of t-LTP in interneurons is induced postsynaptically and can be expressed presynaptically by an increase in glutamate release probability or postsynaptically, by an increase in postsynaptic receptor number or unitary conductance (Le Roux et al., 2013). Because GABAergic inhibition can gate long-term plasticity at glutamatergic synapses, changes in excitatory drive onto hippocampal interneurons have been suggested to have an essential role in stabilizing network excitability and preserving the fidelity of spatio-temporal processing in the brain (Nicholson and Kullmann, 2014).

Muscarinic modulation of STDP of inhibition

Through feedforward or feedback inhibition, GABAergic circuits can control the input–output function of pyramidal neurons by adjusting the precise spike timing required to induce STDP (Pouille and Scanziani, 2001; Maccaferri, 2005). CA1 inhibitory interneurons also receive cholinergic innervation from the medial septum-diagonal band of Broca (Dutar et al., 1995) that activates both mAChRs and nAChRs to modulate interneuron activity (Behrends and ten Bruggencate, 1993; Cea del Rio et al., 2011; Yi et al., 2014). Pharmacological activation of M1Rs reportedly increases the excitability of PV+ interneurons and enhances perisomatic inhibition onto pyramidal cells (Yi et al., 2014), whereas activation of M1Rs in OLM interneurons increases dendritic inhibition onto CA1 and entorhinal cortical neurons (Haam et al., 2018). Recent evidence using optogenetic activation of cholinergic projections reveal an M3R-mediated increase in inhibitory interneuron excitability that decreases CA3-CA1 glutamatergic transmission (Goswamee and McQuiston, 2019). Although the identity of the interneurons was not determined, the requirement for metabotropic GABAB receptors and inwardly rectifying potassium channels on CA1 pyramidal cells suggests the involvement of GABAergic cells that primarily mediate slow inhibition (Szabadics et al., 2007; Fuentealba et al., 2008; Price et al., 2008).

mAChR activation can also directly act at hippocampal GABAergic synapses, exhibiting heterogeneous effects depending on mAChR subtype, presynaptic interneuron identity, hippocampal subregion and age (Dannenberg et al., 2017). Muscarinic receptors were initially shown to depress GABA release in CA1 (Pitler and Alger, 1992; Behrends and ten Bruggencate, 1993), but recent evidence dissecting mAChR subtypes demonstrate a facilitating effect of presynaptic M2/4Rs and M3/5Rs in GABA release via IP3 signaling (Gonzalez et al., 2014). In the CA3 subfield, activation of M2Rs reportedly reduces the amplitude of inhibitory currents from fast-spiking basket and axo-axonic cells (Szabó et al., 2010), although whether M2Rs were presynaptically located was not examined. Moreover, muscarinic signaling can have complex circuit-wide influences to powerfully regulate local network activity. Activation of mAChRs indirectly induces depolarization of a specific type of GABAergic interneurons that express vasoactive intestinal peptide (VIP) and specifically inhibit other interneurons by increasing the inhibitory tone onto PV+ interneurons, thereby disinhibiting principal cells that target VIP+ cells (Bell et al., 2015). When combined with repetitive depolarization, M1Rs induce strong LTP of GABAergic synaptic inputs onto CA1 pyramidal cells (Domínguez et al., 2014). Like M1Rs, evidence also indicates that M3Rs are expressed in hippocampal basket cell interneurons (Cea del Rio et al., 2010) whose activation can regulate the GABAergic efficacy (Lawrence et al., 2006).

Like excitatory synapses, plasticity at inhibitory synapses in the hippocampus can be induced by repetitively pairing pre- and postsynaptic activity (Ormond and Woodin, 2009; Kullmann and Lamsa, 2011). Depending on the induction protocol, plasticity may be expressed presynaptically (Ahumada et al., 2013) or postsynaptically (Ormond and Woodin, 2011).

Near coincident pre- and postsynaptic activity (±1 ms) reduces the strength of GABAergic responses by changing the chloride driving force in hippocampal pyramidal neurons (Ormond and Woodin, 2009) and its induction efficacy is sensitive to whether GABAergic postsynaptic responses are hyperpolarizing or depolarizing (Balena et al., 2010). Furthermore, this form of STDP at GABAergic synapses can increase the magnitude of glutamatergic synaptic transmission and is referred to as disinhibition-mediated LTP (Ormond and Woodin, 2009; Takkala and Woodin, 2013). Activation of mAChRs prevents timing-dependent attenuation of GABAergic inhibition and the consequent disinhibition-mediated LTP (Takkala and Woodin, 2013). The underlying mechanisms are unclear but may involve a reduction in GABA release via presynaptic M2-type mAChRs. Interestingly, M2-type mAChRs on GABAergic terminals are critical in another form of inhibitory STDP. In this case, Hebbian pre-post pairing of activity triggers t-LTD at GABAergic synapses in rat CA1, that is accompanied by a decrease in GABA release (Ahumada et al., 2013). This t-LTD of inhibition requires type 1 cannabinoid receptors (CB1Rs) and M2-type mAChRs that synergistically regulate presynaptic cAMP/PKA signaling, providing a novel mechanism by which cholinergic activity regulates GABAergic synaptic plasticity.

Coordinated interplay between mAChRs and other G protein-coupled receptors may be a common theme in neuromodulation of synaptic plasticity. We recently demonstrated that activation of mAChRs primes mGluR-dependent inhibitory LTP at CA1 GABAergic synapses (Morales-Weil et al., 2020). The cooperative action of mAChRs and mGluRs in the induction of inhibitory LTP is dependent on consecutive activation of M1Rs and mGluR1/5, which may be related to the generation and synchronization of brain oscillation patterns in different behavioral states. Similar synergism of mGluRs and M1Rs in the induction of LTP at excitatory synapses onto stratum oriens interneurons has also been demonstrated (Duigou et al., 2015). mAChRs and mGluRs can also cooperatively participate in a long-term enhancement of burst firing in the subiculum (Moore et al., 2009), which may have subsequent effects on spike-timing dependent plasticity. In the neonatal hippocampus, repetitive pre and postsynaptic depolarization transiently depresses GABA release that was dependent on both mGluR and mAChR activation (Taketo and Matsuda, 2017). Other neuromodulatory systems can also interact with cholinergic signaling to regulate timing-dependent synaptic plasticity. For example, activation of dopamine (DA) receptors, via cAMP pathways, can convert mAChR-dependent t-LTD (Brzosko et al., 2019, 2017), as well as conventional LTD (Brzosko et al., 2015), into potentiation. Thus, ACh and DA may act in opposing manners to regulate the directionality of activity-dependent synaptic plasticity, which may optimize reinforcement learning in dynamic environments, by reducing and potentiating synapses linked to negative and rewarding outcomes, respectively (Zannone et al., 2018).

Wired vs volume transmission for cholinergic signaling

Cholinergic neurons project widely and diffusely throughout the brain. The anatomical mismatch between ACh release sites and receptor locations suggests that ACh signaling occurs via volume transmission rather than via traditional synapses (Descarries et al., 1997; Mechawar, 2008). However, the high expression of ACh esterase points to a highly efficient clearing of ACh from the synaptic cleft (Zimmerman and Soreq, 2006). For instance, inhibition of ACh esterase has been a key manipulation for uncovering cholinergic influences in brain function and synaptic plasticity. Moreover, ACh has also been shown to act on a rapid timescale in behavioral tasks that require sub second reactivity (Parikh et al., 2007; Letzkus et al., 2011).

Notably, ACh release can occur in two modes, tonic and phasic, to serve different cognitive functions (Sarter et al., 2009; Teles-Grilo Ruivo and Mellor, 2013). While slowly changing tonic levels of ACh is associated with arousal and brain state transitions, rapid phasic ACh release mediates precisely defined cognitive operations such as signaling reinforcement to guide behavioral learning (Hangya et al., 2015). At the cellular level, tonic and phasic modes of cholinergic transmission may differentially engage distinct subsets of ACh receptor subtypes, each with differing affinities, desensitization characteristics, and cellular localizations. These differences are critical for the control and specificity of cholinergic actions on synapses at the local microcircuit level. However, work examining muscarinic influences on brain plasticity has mostly relied on pharmacological approaches and medial septal lesions that disturb normal ACh levels and dynamics. Stimulation of cholinergic afferents in vivo has yielded both facilitatory and suppressive influences on hippocampal synaptic plasticity (Newlon et al., 1991; Markevich et al., 1997), highlighting the complexity of cholinergic actions in the hippocampus. Future work taking advantage of modern developments to selectively monitor and manipulate neuronal activity and molecular signaling pathways in vivo will be necessary to clarify how muscarinic activity modulates diverse forms of synaptic plasticity to guide adaptive behavior.

FUTURE DIRECTIONS

Over the past decade, STDP has been increasingly demonstrated at both excitatory and inhibitory synapses within the hippocampal formation. Essential properties of STDP point out to synapse-specificity learning rules to coordinate pre- and postsynaptic activity to induce persistent changes in synaptic connections across different synapses types (i.e. EXCITATORY vs Inhibitory synapses). In this review, we have highlighted a diversity of mechanisms by which the cholinergic system particularly mAChR can affect the induction and/or expression of long-term changes at both excitatory and inhibitory synapses (Fig. 2). The emerging evidence of cooperative and dynamic interaction between ACh

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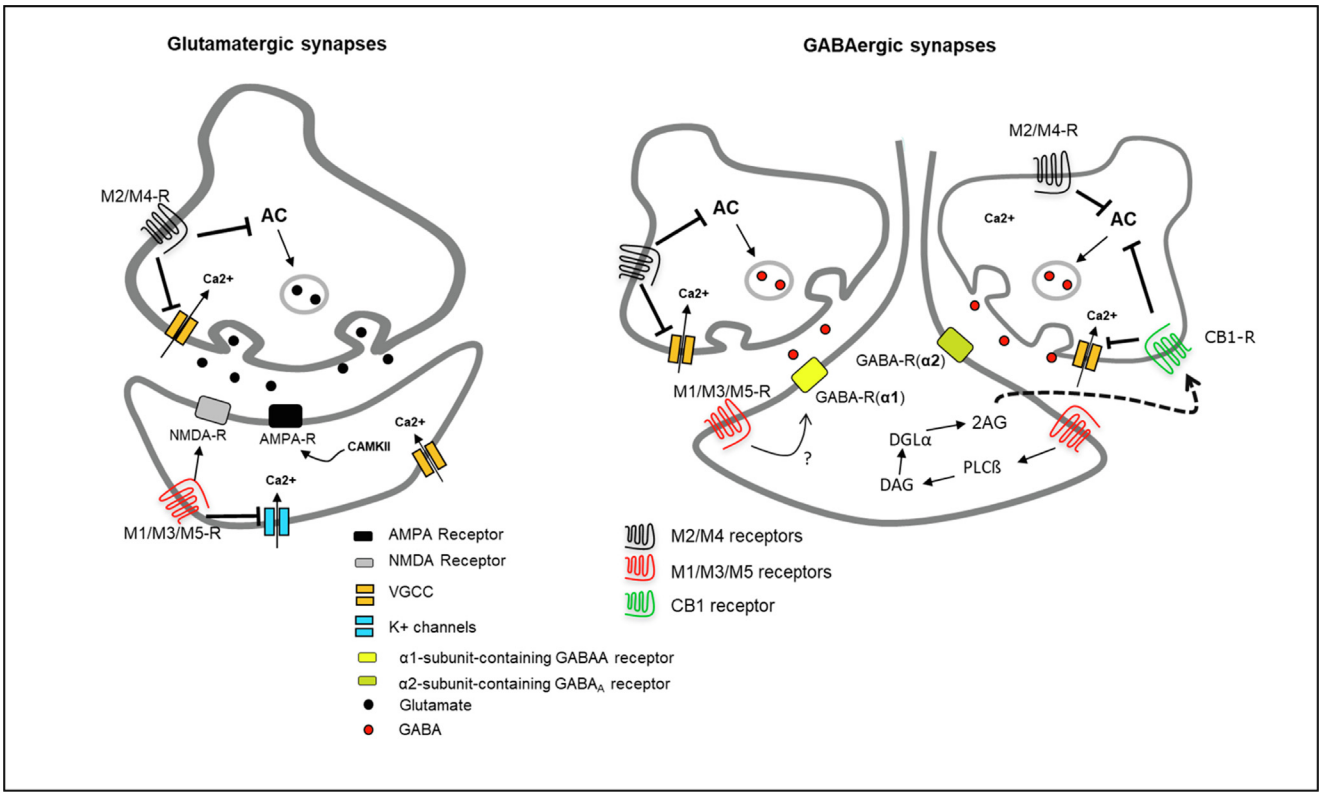

Fig. 2. Schematic representation illustrating the localization and function of mAChRs in the induction of hippocampal short- and long-term plasticity at glutamatergic (left) and GABAergic (right) synapses. mAChRs are expressed in both the pre- and postsynaptic sites and are grouped into M1/M3/M5 or M2/M4 subtypes. At GABAergic synapses, activation of cholinergic neurons and retrograde signaling mediated by endocannabinoids act cooperatively to regulate activity-dependent synaptic plasticity.

and other neuromodulatory system to regulate the directionality of the activity-dependent synaptic plasticity suggests complex and intricate neuromodulatory mechanisms of synapse regulation. Whether the plasticity rules and neuromodulatory interaction described in vitro apply to activity-dependent synaptic modification in vivo requires future investigation. Similarly, how these forms of activity-dependent synaptic plasticity and its modulation by cholinergic system are modified during development and/or pathological conditions need to be determined. We are only beginning to unravel the essential cellular and physiological mechanisms by which the cholinergic system confers an immense computational capability to the hippocampal network in complex cognitive processing such as learning and memory.

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