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MUSCARINIC RECEPTORS, FROM SYNAPTIC PLASTICITY TO ITS ROLE IN NETWORK ACTIVITY.

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ABSTRACT

Acetylcholine acting via metabotropic receptors plays a key role in learning and memory by regulating synaptic plasticity and circuit activity. However, a recent overall view of the effects of muscarinic acetylcholine receptors (mAChRs) on excitatory and inhibitory long-term synaptic plasticity and on circuit activity is lacking. This review focusses on specific aspects of the regulation of synaptic plasticity and circuit activity by mAChRs in the hippocampus and cortex. Acetylcholine increases the excitability of pyramidal neurons, facilitating the generation of dendritic Ca^{2+}-spikes, NMDA-spikes and action potential bursts which provide the main source of Ca^{2+} influx necessary to induce synaptic plasticity. The activation of mAChRs induced Ca^{2+} release from intracellular IP_3-sensitive stores is a major player in the induction of a NMDA independent long-term potentiation (LTP) caused by an increased expression of AMPA receptors in hippocampal pyramidal neuron dendritic spines. In the neocortex, activation of mAChRs also induces a long-term enhancement of excitatory postsynaptic currents. In addition to effects on excitatory synapses, a single brief activation of mAChRs together with short repeated membrane depolarization can induce a long-term enhancement of GABA A type (GABAA) inhibition through an increased expression of GABAA receptors in hippocampal pyramidal neurons. By contrast, a long term depression of GABAA inhibition (**i**LTD) is induced by muscarinic receptor activation in the absence

of postsynaptic depolarizations. This **i**LTD is caused by an endocannabinoid-mediated presynaptic inhibition that reduces the GABA release probability at the terminals of inhibitory interneurons. This bidirectional long-term plasticity of inhibition may dynamically regulate the excitatory/inhibitory balance depending on the quiescent or active state of the postsynaptic pyramidal neurons.

Therefore, acetylcholine can induce varied effects on neuronal activity and circuit behavior that can enhance sensory detection and processing through the modification of circuit activity leading to learning, memory and behavior.

KEYWORDS

Long term potentiation; Calcium spikes; NMDA-spikes; Calcium stores; Enhanced inhibition; Rhythmic activity.

INTRODUCTION

The cholinergic regulation of hippocampal and cortical activity plays a fundamental role in cognitive functions linked with learning and memory (Himmelheber et al., 2000). Acetylcholine (ACh) muscarinic receptors (mAChRs) and nicotinic receptors (nAChRs) can induce plasticity at excitatory and inhibitory synapses and are essential in learning and memory processes. Indeed, lesions of the cholinergic projections from the septum to the hippocampus produce memory and attention deficits and disrupt the normal execution of complex behaviors (Buno and Velluti, 1977).

Cholinergic afferents are distributed at high density throughout all layers of the neocortex in mice and rat, with particularly high densities in cortical layers 1, 5 and 6 (Radnikow and Feldmeyer, 2018). Neurons within the medial septum and nucleus of the vertical limb of the diagonal band provide the major cholinergic innervation of the hippocampus (Haam and

Yakel, 2017). Of the mAChRs family mainly M1, M2 and M4 are expressed in the neocortex, although M4 has a considerable lower expression. M1, M2, M3 and M4 mAChRs are expressed in the hippocampus. In the rodent neocortex, immunoreactive staining of mAChRs shows a strong laminar pattern (Levey et al., 1991). M1 mAChR immuno-reactivity is present in most cortical neurons and particularly dense in layer 2/3 and layer 6. M2 protein is dense in layer 4 and in the border of layer 5/6. M4 mAChR immunoreactivity is localized in layer 2/3, layer 4 and layer 5. In the human neocortex, highest densities of M1, M2 and M3 mAChRs is observed in superficial layers of most cortical (Vanderheyden et al., 1990, Scarr et al., 2016, Obermayer et al., 2017).

mAChR activation can lead to a broad range of actions. It mediates hyperpolarization, depolarization or combinations of both, increases neuronal excitability and decreases spike-frequency adaptation. All these effects add with the mAChR mediated enhancement of excitatory synaptic responses and assists long-term potentiation (LTP) of glutamatergic synaptic transmission both in the cortex and hippocampus and of GABAergic inhibition in the (Oldford and Castro-Alamancos, 2003, Fernandez de Sevilla and Buno, 2010, Barros-Zulaica et al., 2014, Dominguez et al., 2014, 2016, 2017). The aim of the present review is to analyze the effects mediated by the activation of mAChRs on both excitatory and inhibitory synaptic transmission and its role in the regulation of circuit activity in the hippocampus and cortex.

REGULATION OF GLUTAMATERGIC SYNAPTIC PLASTICITY BY mAChR

This section considers recent findings on glutamatergic synaptic plasticity mediated by the activation of metabotropic cholinergic receptors in pyramidal cells of hippocampus and cortex. These cholinergic effects can

be generated both *via* pre- or postsynaptic mechanisms.

Presynaptically, Excitatory synapses between CA3 and CA1 pyramidal neurons are presynaptically inhibited by ACh, *via* activation of mAChRs (Hounsgaard, 1978, Fernandez de Sevilla et al., 2002, Fernandez de Sevilla and Buno, 2003). In hippocampal slices of juvenile rats this effect is mediated by a reduction of glutamate release at the terminals of SCs (Buno et al., 2006, Cabezas and Buno, 2006, 2011), caused by the inhibition of voltage-gated Ca^{2+} channels (VGCC) *via* a G-protein-coupled signaling pathway (Qian and Saggau, 1997). This presynaptic inhibition is absent in a special type of synapses in the hippocampus of young rats called *silent* synapses, as demonstrated by *in vitro* recordings of synaptic currents evoked in CA1 pyramidal by 'minimal' stimulation of SCs, which activates one or very few synapses (Fernandez de Sevilla et al., 2002, Cabezas and Buno, 2006, 2011). Newly created synapses only express NMDA receptors (NMDARs) and are *silent* because they do not conduct at the resting membrane potential and only transmit when the postsynaptic neuron is depolarized, relieving the voltage-dependent block by extracellular magnesium of NMDARs. When synapses also expressing AMPA receptors (AMPARs) develop with synapse maturation, synapses conduct irrespective of the membrane potential of the postsynaptic neuron, becoming *functional*. Activation of mAChRs reduces the probability of glutamate release from the presynaptic terminals of *functional* but not of *silent* synapses, causing a selective maturation-dependent regulation of the non-NMDA mediated synaptic transmission (Liao et al., 1995, Gasparini et al., 2000, Fernandez de Sevilla et al., 2002, Cabezas and Buno, 2006, 2011)

Therefore, terminals of *functional* synapses have the molecular machinery required for the presynaptic inhibition, whereas this machinery is absent in terminals of *silent* synapses. In this scenario, cholinergic input could disconnect mature *functional* synapses while favoring transmission

through immature *silent* synapses, thus facilitating activity-dependent plastic phenomena mediated *via* NMDAR activation at *silent* synapses.

Postsynaptically, mAChR activation inhibits several potassium channels increasing the input resistance and depolarizing neurons (Dutar and Nicoll, 1988). M1 and M3 mAChRs are coupled to phospholipase C (PLC) *via* G-proteins (Gq/11). The activation of PLC catalyzes the phosphatidylinositol 4, 5- bisphosphate hydrolysis and inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol are produced (Abe et al., 1992, Burford et al., 1995, Ishii and Kurachi, 2006). IP_3 receptor (IP_3R) activation induces Ca^{2+} release from endoplasmic reticulum (ER) stores (Rose and Konnerth, 2001). It has been shown that M1 and M3 mAChR activation triggers the production of IP_3 and Ca^{2+} release from the ER in CA1 pyramidal neurons, resulting in LTP at SC synapses, which is also induced by intracellular IP_3 uncaging. A Ca^{2+} wave that rapidly propagates along the apical dendritic shaft towards the soma of pyramidal neurons characterizes the ACh-mediated Ca^{2+} release from the ER (Fernandez de Sevilla et al., 2008, Fernandez de Sevilla and Buno, 2010). This LTP is NMDAR independent and is expressed postsynaptically by an increase of AMPARs in spines and an enhanced NMDA response. Both AMPA- and NMDA-response enhancements follow a similar time course. Theoretically, the enhanced NMDAR-mediated transmission could lead to strong depolarization and Ca^{2+} influx, reducing the threshold and increasing the magnitude of LTP. However, in older animals, mAChR activation induces a robust NMDAR-dependent strengthening of glutamatergic synapses in CA1 pyramidal neurons (Dennis et al., 2016).

Activation of mAChRs can induce transient Ca^{2+} elevations in CA1 astrocytes in hippocampal slices (Araque et al., 2002). This Ca^{2+} rise can induce glutamate release to produce LTP *in vivo* by acting at the presynaptic terminal of the CA3-CA1 synapses (Navarrete et al., 2012). This LTP

requires the temporal coincidence of the astrocyte Ca^{2+} rise and a mild postsynaptic depolarization, suggesting a retrograde signaling from the postsynaptic neuron to induce the presynaptic expression of LTP (see Araque et al. in this Issue). Thus, several forms of LTP can be induced by mAChR activation depending on brain maturation (Figure 1).

In layer 5 pyramidal neurons of the barrel cortex ACh acting through nAChRs and M1 subtype mAChRs induces LTP, of excitatory postsynaptic currents and through nAChRs and M2 subtype mAChRs receptors reduces inhibitory postsynaptic currents in slices (Nunez et al., 2012). These effects increase excitability and contribute to the generation of Ca^{2+} spikes when inputs in basal dendrites of layer 5 pyramidal neurons are stimulated. In addition, the release of ACh by basal forebrain stimulation *in vivo* induces an long-lasting enhancement in the response to vibrissa deflection of layer 5 barrel cortex neurons (Diez-Garcia et al., 2017). Therefore, ACh increases the excitatory/inhibitory balance and induces a switch of the synaptic responses from single spikes to a bursting output mode; effects with possible consequences for plastic properties and sensory processing (Sanchez-Vives and McCormick, 2000, Rigas and Castro-Alamancos, 2009, Nunez et al., 2012).

Slow dendritic spikes and synaptic plasticity. Due to their complex geometries and electrical properties, dendrites of pyramidal hippocampal and cortical neurons can perform complicated operations with their synaptic inputs (Golding et al., 2002). Synaptic inputs can trigger dendritic responses due to activation of VGCC termed dendritic Ca^{2+} spikes (Hausser et al., 2000, Bonansco et al., 2002, Nunez et al., 2012). Another important source of Ca^{2+} is caused by the synaptic activation of NMDARs, which due to their Ca^{2+} permeability and voltage-dependent properties can also trigger slow active dendritic responses termed NMDA-spikes (Schiller and Schiller, 2001, Bonansco and Buno, 2003, Nunez et al., 2012). Both dendritic Ca^{2+}-

spikes and NMDA-spikes are of crucial importance because they provide the main source of Ca^{2+} influx necessary to induce synaptic plasticity. Ca^{2+}- and NMDA-spikes can remain confined to the dendritic branch in which they are generated, or can trigger widespread activity. While both local and global forms of dendritic computations have been observed *in vitro* and *in vivo* (Goldberg and Yuste, 2005, Beaulieu-Laroche et al., 2019), it is not clear how they contribute to circuit activity and synaptic plasticity.

Activation of excitatory synaptic inputs can trigger dendritic Ca^{2+}- and NMDA-spikes and action potential bursts *in vitro* both in hippocampal and cortical pyramidal neurons when inhibition is reduced or when cholinergic activity is enhanced (Diez-Garcia et al., 2017). Consequently, ACh may facilitate dendritic Ca^{2+}-mediated responses favoring synaptic plasticity and modifying circuit activity (see below). In addition, rhythmic NMDA-spikes can be triggered by tetanic stimulation of Schaffer collaterals and by brief iontophoretic pulses of NMDA *in vitro* in hippocampal CA1 pyramidal neurons (Bonansco et al., 2002, Bonansco and Buno, 2003).

REGULATION OF PLASTICITY AT GABAERGIC SYNAPSES BY mAChR.

Research on synaptic plasticity has fundamentally focused on LTP and and long-term depression (LTD) at excitatory synapses on pyramidal cells of the hippocampus and cortex (in this Special Issue and above). However, evidence has accumulated indicating that synaptic inhibition is also plastic and that its regulation is vital given that inhibition controls: plasticity at excitatory synapses; network operation and; the excitatory/inhibitory balance; ultimately contributing to information processing and storage (Galvan et al., 2011, Chiu et al., 2019).

Several types of inhibitory interneurons are present in the hippocampus and cortex that connect to specific somatic and dendritic

domains on pyramidal neurons (Bartos and Elgueta, 2012, Bezaire and Soltesz, 2013, Tremblay et al., 2016, Pelkey et al., 2017, Feldmeyer et al., 2018). The inhibitory transmitter GABA released by interneurons acts through several types of postsynaptic $GABA_AA$ type receptors ($GABA_ARs$). The $GABA_ARs$ responsible for phasic inhibition on pyramidal neurons are predominantly made up by β_2 and β_3 subunits in combination with receptors expressing $\alpha_6\beta\delta$ and $\alpha_5\beta\gamma_2$ subunits. The presynaptic and extrasynaptic GABAARs mediating tonic inhibition contain $\alpha_6\beta\delta$ and $\alpha_5\beta\gamma_2$ subunits (Farrant and Nusser, 2005, Brickley and Mody, 2012). In addition, $GABA_B$ receptors are mainly found in presynaptic terminals of inhibitory interneurons (Misgeld et al., 1995, McBain and Kauer, 2009, Castillo et al., 2011).

This Review considers recent findings on GABAergic synaptic plasticity, focusing mainly on the cellular mechanisms that mediate the cholinergic regulation of LTP and LTD of inhibitory transmission in pyramidal cells of hippocampus and cortex.

Activity-dependent LTP and LTD of synaptic inhibition. Activity-dependent synaptic plasticity serves as a mechanism for processing and storing information and regulating neuronal development. In addition, changes in the intrinsic properties of neurons can be modified in activity-dependent manner to enable learning and development. Both presynaptic and postsynaptic mechanisms may underlie activity-dependent synaptic plasticity of GABAergic transmission. Presynaptic-mediated plasticity of $GABA_A$ inhibition has been previously extensively reviewed (Misgeld et al., 1995, McBain and Kauer, 2009, Castillo et al., 2011), therefore, we will focus on inhibitory plasticity mediated postsynaptically.

Several forms of activity-dependent postsynaptic-mediated inhibitory plasticity have been reported. Importantly, it has been shown that a lasting

increase in the activity of pyramidal cells is functionally opposed by an increased inhibition to bring cellular output back to baseline levels (Chiu et al., 2019). Presynaptic and mixed presynaptic-postsynaptic causes have also been shown to mediate this homeostatic process (Gainey and Feldman, 2017).

Long-term facilitation of $GABA_A$ inhibition by mAChRs. It has been shown that in young rats a single brief pulse of ACh or stimulation of cholinergic septal fibers (CSF) with a brief pulse barrage, combined with short postsynaptic depolarization repeated throughout the experiment, induces a long-term enhancement of $GABA_A$ inhibition in CA1 pyramidal neurons of the rat hippocampus (Dominguez et al., 2014, 2016, 2017). This enhanced inhibition, termed $GABA_A$-LTP, is remarkably fast and strong and once established persists even after stopping the repeated postsynaptic depolarization. However, postsynaptic depolarization in the absence of ACh does not modify IPSPs.

The $GABA_A$-LTP is prevented by pirenzepine, suggesting that activation M1-suptype mAChRs is required, and is markedly reduced by L-655,708, an inverse agonist of $\alpha_5\beta\gamma_2$-$GABA_A$Rs, suggesting that the $GABA_A$-LTP is mediated by an increased activation of $\alpha_5\beta\gamma_2$ subunit-containing $GABA_A$Rs (Dominguez et al., 2014, 2016). Intracellular loading with the Ca^{2+} chelator BAPTA inhibits the $GABA_A$-LTP, which is also prevented by inhibition of L-type VGCC, suggesting that an increase in cytosolic Ca^{2+} mediated by Ca^{2+} influx through L-type VGCC is required (Dominguez et al., 2014).

In the absence of postsynaptic depolarization, ACh triggers a prolonged presynaptic depolarization-induced suppression of inhibition (DSI). This sustained DSI results in LTD of inhibition (**i**LTD) that is prevented by superfusion with AM-251, a specific type 1 endocannabinoid (eCB) receptor (eCB_1R) antagonist/inverse agonist. AM-251 also induced a

significant increase of the $GABA_A$-LTP, suggesting that ACh triggered the release of eCBs from the postsynaptic CA1 pyramidal neuron, which caused the **i**LTD by retrograde activation CB_1Rs at inhibitory interneuron terminals (Dominguez et al., 2014). Even though **i**LTD and $GABA_A$-LTP concur, the smaller **i**LTD is dominated by the much stronger $GABA_A$-LTP. Taken together these results suggest that both ACh and membrane depolarization are prerequisites for the induction of the $GABA_A$-LTP and that ACh is capable of triggering **i**LTD in isolation or **i**LTD and $GABA_A$-LTP jointly in function of the quiescent or active state, respectively of the postsynaptic neuron.

G-protein–coupled receptors (GPCRs), are known to trigger LTP of excitatory synaptic transmission in hippocampal and cortical pyramidal neurons (this Chapter and (Cohen and Abraham, 1996, Nunez et al., 2012, Teles-Grilo Ruivo and Mellor, 2013, Dennis et al., 2016)), and could participate in the induction of the $GABA_A$-LTP. Indeed, blockade of GPCRs by intracellular loading with GDPβS abolished the $GABA_A$-LTP, indicating that G-protein activation is essential. By contrast, GDPβS loading did not modify control IPSCs (Dominguez et al., 2014). The strong Ca^{2+} rise triggered by M1 subtype mAChR activation and by the imposed postsynaptic depolarization can stimulate PKC, PKA and CAMKII, which have been shown to be involved in synaptic plasticity (Costa-Mattioli et al., 2009, Kowalski et al., 2016, Mahajan and Nadkarni, 2019). Blockade of PKA, PKC and CaMKII inhibited the $GABA_A$-LTP, suggesting that those kinases contribute to the plasticity of inhibition (Dominguez et al., 2014).

In this scenario, the $GABA_A$-LTP can operate as a homeostatic negative feedback mechanism to control abnormal hyperexcitable states in the CA1 network, thereby preventing strong detrimental Ca^{2+} influx (see below). In addition, the **i**LTD can facilitate the induction of dendritic Ca^{2+} spikes and NMDA-spikes and action potential bursts, thus favoring the Ca^{2+}

influx required to induce LTP at excitatory synapses. Theoretically, PKA activation through Ca^{2+}/calmodulin-stimulated adenylyl cyclase, which is essential in the genesis of LTP and memory formation (Poser and Storm, 2001), can act as a coincidence detector for the induction of the $GABA_A$-LTP (Figure 2).

Importantly, the $GABA_A$-LTP is not modified by imposed modification of the Cl^- gradient nor paralleled by changes in the Cl^- reversal potential (Dominguez et al., 2014, 2016), as occurs in other forms of potentiation of $GABA_A$ synapses (Woodin et al., 2003, Rivera et al., 2004), suggesting that changes in the intracellular Cl^- concentration do not contribute to the $GABA_A$-LTP.

The temporal progression of the $GABA_A$-LTP is matched by a decreased IPSC decay slope, an increased tonic GABA current, strong outward rectification and is markedly reduced by L-655,708, suggesting that the $GABA_A$-LTP is caused by a rapid increase in the number of $\alpha_5\beta\gamma_2$-$GABA_A$Rs activated by the GABA released (Dominguez et al., 2014, 2016, 2017). An alternative possibility is that more extrasynaptic $\alpha_5\beta\gamma_2$-$GABA_A$Rs are activated by GABA "spillover". Although a direct demonstration of GABA spillover has not been provided, it appears unlikely (Dominguez et al., 2014).

Schaffer collateral stimulation can trigger GABA release from both cholecystokinin positive (CCK^+) and parvalbumin positive (PV^+) interneuron terminals (Bartos and Elgueta, 2012, Bezaire and Soltesz, 2013, Tremblay et al., 2016, Pelkey et al., 2017, Feldmeyer et al., 2018). CCK^+ interneurons innervate the proximal dendritic regions of pyramidal neurons in the hippocampus where $\alpha_5\beta\gamma_2$-$GABA_A$Rs are concentrated (Serwanski et al., 2006) and PV^+ cells innervate the somatic regions of those cells and show precise synchronous release (Savanthrapadian et al., 2014). Superfusion of

ω-*conotoxin GVIA*, that specifically inhibit GABA release from CCK^+ interneurons, or ω-*agatoxin*, which specifically inhibits GABA release from PV^+ interneurons (Hefft and Jonas, 2005), reduced the $GABA_A$-LTP, suggesting that both interneuron types contribute to the inhibitory synaptic plasticity (Dominguez et al., 2014).

Functional consequences: regulation of the excitatory/inhibitory balance. As mentioned above, synaptic plasticity is thought to be essential for learning and memory processes, but plasticity of a given input must be coordinated with other synapses to conserve the excitatory/inhibitory balance in the circuit. If LTP is induced the increased excitation might unbalance the relationship between excitation and inhibition leading to abnormal hyperexcitable states and detrimental Ca^{2+} influx. Although this scenario favors plasticity at excitatory synapses it also makes the system unstable, a risky situation that could lead to abnormal circuit behavior due to unbalance caused by the increased excitatory/inhibitory balance (Carcea and Froemke, 2013, Bonansco and Fuenzalida, 2016). However, the system has strong safety mechanisms because a long-term enhancement of the strength of synaptic inhibition can restore the excitatory/inhibitory balance in circuits where LTP is induced, thus preventing abnormal states

Besides synaptic mechanisms the up- or down-regulation of the slow Ca^{2+}-dependent after hyperpolarization (sAHP) in hippocampal pyramidal neurons (Borde et al., 1995, Borde et al., 1999, Power et al., 2001, Carrer et al., 2003) can theoretically hinder or assist, respectively GABAergic plasticity in hippocampal circuits. A strong sAHP can reduce the depolarization required for the induction of the $GABA_A$-LTP, whereas a reduced sAHP would have the opposite effect.

It has been repeatedly shown that ACh, acting through muscarinic receptors, can facilitate the induction of LTP at excitatory glutamatergic synapses in pyramidal neurons of hippocampus and cortex (Teles-Grilo

Ruivo and Mellor, 2013, Dennis et al., 2016). The muscarinic LTP of excitation and the $GABA_A$-LTP are triggered by comparable molecular mechanisms and concur in hippocampal pyramidal neurons. It has been shown that both the enhancement of glutamate synapses and the negative feedback homeostatic inhibitory process can be triggered through common postsynaptic molecular pathways (see above and (Huang et al., 2005, Turrigiano, 2012, Carcea and Froemke, 2013, Froemke, 2015, Chiu et al., 2019)). In addition, the LTP of glutamatergic synapses and the $GABA_A$-LTP display comparable magnitude and time course, suggesting that a precise homeostatic regulatory mechanism may be at work in the system (Fernandez de Sevilla et al., 2008, Dominguez et al., 2014). Similar findings have been reported in other systems (Shu et al., 2003, Gainey and Feldman, 2017).

In CA1 pyramidal neurons spike timing dependent plasticity (STDP) can simultaneously induce LTP at excitatory and **i**LTD at inhibitory synapses in hippocampal CA1 pyramidal neurons (Ahumada et al., 2013). This **i**LTD requires coordinated eCB release, causing activation of presynaptic type 1 eCB receptors (eCB_1Rs), and of muscarinic receptors, which mediate a decreased probability of GABA release from inhibitory interneuron terminals. In Layer 5 pyramidal neurons of the rat barrel cortex ACh acting through M1-mAChRs enhances excitatory postsynaptic currents, and through nAChRs and M2 mAChRs reduces inhibitory postsynaptic currents (Nunez et al., 2012, Ahumada et al., 2013, Diez-Garcia et al., 2017), indicating that the glutamatergic LTP and the $GABA_A$-LTP can be triggered simultaneously through comparable mechanisms. Interestingly, prolonged sensory deprivation can trigger a remodeling of inhibitory cortical synapses leading to IPSPs with faster decay kinetics and larger amplitudes. This homeostatic synaptic transformation would oppose the effects of the reduced sensory input to restore the normal excitatory/inhibitory balance in the circuit (Li et al., 2009). A presynaptic plasticity of inhibition can also contribute in

restoring the excitatory/inhibitory balance (in this Special Issue and (Castillo et al., 2011, Monday et al., 2018)).

The excitatory/inhibitory balance also plays a key role in neural coding because if excitation dominates it leads to high activity levels and information content, however if inhibition dominates it leads to suppressed activity with low information content in the network (Deneve and Machens, 2016, Zhou and Yu, 2018). Indeed, long-term changes in EPSP strength are relevant functionally if they modify firing activity in the circuit (Marder and Buonomano, 2004) and have been experimentally related with memory processes (Costa-Mattioli et al., 2009, Nabavi et al., 2014). However, how excitatory and inhibitory synapses are modified in an organized manner to induce the circuit modifications that sustain learning and memory processes is far from being understood and is the *new frontier* of neuroscience (Humeau and Choquet, 2019).

REGULATION OF CIRCUIT ACTIVITY BY mAChRs

Effects of ACh at the circuit level. ACh levels in the hippocampus and neocortex increase dramatically during arousal and attentional states and can modify the activity of pyramidal neurons (Himmelheber et al., 2000, Teles-Grilo Ruivo et al., 2017). High ACh levels acting through nAChRs and mAChRs enhance the responses evoked by sensory stimulation, while low ACh concentrations acting through mAChRs can contribute to memory consolidation (Hasselmo and McGaughy, 2004). In addition, ACh can shift the discharge pattern of pyramidal neurons from a single spiking to a bursting firing mode, a change mediated through Ca^{2+}- and/or NMDA-spikes, that assist the retrograde propagation of action (Power and Sah, 2008, Nunez et al., 2012). Ca^{2+} spikes, NMDA-spikes and action potential bursts invade dendritic fields causing a rapid increase in Ca^{2+} concentration in dendritic spines that regulates circuit operation and facilitates synaptic plasticity, with

important consequences in sensory processing, memory and learning.

ACh regulates rhythmic activity in the hippocampus and cortex. ACh is released tonically in the hippocampus from the septum and diagonal band of Broca during arousal, the performance of cognitively demanding tasks and REM sleep (Zhang et al., 2010). The septo-hippocampal projection is essential for triggering the rhythmic network oscillations at 4–10 Hz called hippocampal theta rhythm (Gaztelu and Buno, 1982), which has been related with learning and memory (Hasselmo and McGaughy, 2004, Vertes, 2005) and with the timing of complex behaviors (Buno and Velluti, 1977).

Intracellular recordings during hippocampal theta *in vivo* show that the membrane potential of hippocampal neurons oscillates at theta frequencies. This "*intracellular theta*" rides on a sustained depolarization and consists in rhythmic EPSPs (Nunez et al., 1987) and IPSPs (Hangya et al., 2009) evoked by rhythmic firing medial septum and diagonal band of Broca neurons (Nunez et al., 1990). Large intracellular theta and sustained depolarization amplitudes can trigger slow spikes and rhythmic action potential bursts, boosting the membrane potential oscillations and assisting action potential backpropagation (Nunez et al., 1987, 1990). In addition, as shown *in vitro* intrinsic membrane properties can support theta-like oscillations to contribute to the genesis theta oscillations in hippocampal pyramidal neurons (Garcia-Munoz et al., 1993).

It was further found that M1 muscarinic receptors in pyramidal neurons but not interneurons play a critical role in cholinergic modulation of hippocampal synaptic plasticity and theta generation (Gu et al., 2017). The in vitro results were further substantiated by in vivo observations of reduced theta power and impaired Y-Maze performance in mice with selective receptor knockout M1 in pyramidal neurons. Other cholinergic receptors, such as nicotinic or muscarinic M4 receptors, may have also contributed to cholinergic-dependent theta generation (Stoiljkovic et al., 2016, Gu et al.,

2017) .M4 receptors likely act through interneurons as their expression is enriched in nonpyramidal neurons (Levey et al., 1991)

Cholinergic agonists and acetylcholinesterase inhibitors can also induce gamma oscillations –i.e., network oscillations in the 30–100 Hz range- in the neocortex and hippocampus *in vitro* (Spencer et al., 2010, Betterton et al., 2017) and *in vivo* (Cape et al., 2000, Rodriguez et al., 2004). Rhythms in the gamma range can establish synchronization of distributed neural responses throughout the brain (Singer, 1999). Gamma oscillations are critical in attention, sensory processing (Fries et al., 2001, Womelsdorf et al., 2006, Howe et al., 2017) and long-term memory (Buzsaki and Draguhn, 2004, Buzsaki and Wang, 2012). In the hippocampus, gamma oscillations can coincide with theta oscillations (Buzsaki et al., 1992, Lisman and Jensen, 2013). In the neocortex, gamma oscillations are induced by different stimuli or tasks, and are related to several cognitive capacities (Fries et al., 2007). Cholinergic agonists and acetylcholinesterase inhibitors can also induce gamma oscillations –i.e., network oscillations in the 30–100 Hz range- in the neocortex and hippocampus *in vitro* (Spencer et al., 2010, Betterton et al., 2017) and *in vivo* (Cape et al., 2000, Rodriguez et al., 2004). Results reveal that ACh enhances gamma oscillation in the hippocampus by acting primarily through muscarinic M1 receptors (Fisahn et al., 2002, Betterton et al., 2017). Gamma oscillations are critical in attention, sensory processing (Fries et al., 2001, Womelsdorf et al., 2006, Howe et al., 2017) and long-term memory (Buzsaki and Draguhn, 2004, Buzsaki and Wang, 2012). In the hippocampus, gamma oscillations can coincide with theta oscillations (Buzsaki et al., 1992, Lisman and Jensen, 2013). In the neocortex, gamma oscillations are induced by different stimuli or tasks, and are related to several cognitive capacities (Fries et al., 2007). Rhythms in the gamma range can establish synchronization of distributed neural responses throughout the brain (Singer, 1999).

ACh and information processing. The following cholinergic effects observed in the cortex *in vivo* should be highlighted: (*i*) high ACh levels increase the magnitude of afferent input through activation of nAChRs located presynaptically on thalamo-cortical terminals (Disney et al., 2007); (*ii*) high ACh levels acting through mAChRs reduce cortico-cortical excitatory recurrent interactions through presynaptic inhibition of glutamate release (Hasselmo and Bower, 1992, Eggermann and Feldmeyer, 2009); (*iii*) stimulation of mAChRs depolarizes and increases neuronal excitability and responsiveness for several minutes (Metherate et al., 1988, Oldford and Castro-Alamancos, 2003); (*iv*) stimulation of mAChRs reduces spike frequency adaptation by inhibiting the K^+-mediated M-current and the sAHP (McCormick and Prince, 1986, Hasselmo and Giocomo, 2006). Consequently, the mAChR-mediated depolarization boosts responses and increases the signal-to noise ratio in the sensory cortex, thereby enhancing response reliability.

In vivo recordings demonstrate that electrical stimulation of the basal forebrain, the main origin of cholinergic fibers, triggers an atropine-sensitive enhancement of responses evoked by vibrissa deflection in layer 5 neurons that is mainly due to an enhanced NMDA-mediated response (Nunez et al., 2012, Barros-Zulaica et al., 2014, Chaves-Coira et al., 2018). The strong Ca^{2+} signal associated with NMDA receptor activation triggers LTP, increasing sensory detection and processing (Alenda and Nunez, 2007, Hasselmo and Sarter, 2011, Barros-Zulaica et al., 2014, Nabavi et al., 2014) and regulates whisking (de Kock and Sakmann, 2009) (Figure 3).

ACh also regulates information processing in the primary visual cortex not only by regulating the magnitude of the visual response, but also the selectivity to stimulus-features such as orientation, direction, and size (Herrero et al., 2008, Soma et al., 2013). Repetitive electrical stimulation of fibers from the lateral geniculate nucleus to the primary visual cortex induce

LTP in the cortex that is enhanced by stimulation of the basal forebrain area through activation of mAChRs (Yan and Zhang, 2005, Dringenberg et al., 2007). ACh also increases the auditory responses of cortical neurons in a non-specific manner (Jimenez-Capdeville and Dykes, 1996). Moreover, learning-induced cortical plasticity is augmented by cortical application of ACh and conversely, prevented by cortical application of the muscarinic antagonist, atropine, during the conditioning (Ji and Suga, 2003, Chen et al., 2004).

CONCLUDING REMARKS

The above reviewed studies demonstrate that ACh, acting through the activation of mAChRs, can enhance excitatory synaptic responses and modify the discharge pattern of hippocampal and cortical pyramidal neurons through the generation of both dendritic Ca^{2+}- and NMDA-spikes. These spikes trigger action potential bursts that propagate through dendritic regions assisting the influx of Ca^{2+} in spines required to induce long-term synaptic plasticity. ACh-induced Ca^{2+} release from the ER also contributes to the long-term synaptic enhancement. The ACh-mediated Ca^{2+} elevations in astrocytes can also assist the neuronal long-term effects through the release of gliotransmitters.

Although the increased excitation caused by ACh and LTP favors plasticity at hippocampal and cortical excitatory synapses it also makes the system unstable and can lead to abnormal hyperexcitable states. However, the system has strong safety mechanisms to offset this risky situation and restore the excitatory/inhibitory balance thorough a rapid long-term enhancement of the strength of synaptic inhibition. In addition, ACh can induce an endocannabinoid-mediated LTD of inhibition. These homeostatic feedback mechanisms control the circuit in function of the degree of activity, ultimately dynamically up-or-down regulating the excitatory/inhibitory

balance. Therefore, the cellular effects of ACh can support the sustained cellular changes that induce the circuit modifications that can ultimately modify behavior.

REFERENCES

Abe T, Sugihara H, Nawa H, Shigemoto R, Mizuno N, Nakanishi S (1992) Molecular characterization of a novel metabotropic glutamate receptor mGluR5 coupled to inositol phosphate/Ca2+ signal transduction. The Journal of biological chemistry 267:13361-13368.

Ahumada J, Fernandez de Sevilla D, Couve A, Buno W, Fuenzalida M (2013) Long-term depression of inhibitory synaptic transmission induced by spike-timing dependent plasticity requires coactivation of endocannabinoid and muscarinic receptors. Hippocampus 23:1439-1452.

Alenda A, Nunez A (2007) Cholinergic modulation of sensory interference in rat primary somatosensory cortical neurons. Brain Res 1133:158-167.

Araque A, Martin ED, Perea G, Arellano JI, Buno W (2002) Synaptically released acetylcholine evokes Ca2+ elevations in astrocytes in hippocampal slices. The Journal of neuroscience : the official journal of the Society for Neuroscience 22:2443-2450.

Barros-Zulaica N, Castejon C, Nunez A (2014) Frequency-specific response facilitation of supra and infragranular barrel cortical neurons depends on NMDA receptor activation in rats. Neuroscience 281:178-194.

Bartos M, Elgueta C (2012) Functional characteristics of parvalbumin- and cholecystokinin-expressing basket cells. The Journal of physiology 590:669-681.

Beaulieu-Laroche L, Toloza EHS, Brown NJ, Harnett MT (2019) Widespread and Highly Correlated Somato-dendritic Activity in Cortical Layer 5 Neurons. Neuron 103:235-241 e234.

Betterton RT, Broad LM, Tsaneva-Atanasova K, Mellor JR (2017) Acetylcholine modulates gamma frequency oscillations in the hippocampus by activation of muscarinic M1 receptors. The European journal of neuroscience 45:1570-1585.

Bezaire MJ, Soltesz I (2013) Quantitative assessment of CA1 local circuits: knowledge base for interneuron-pyramidal cell connectivity. Hippocampus 23:751-785.

Bonansco C, Buno W (2003) Cellular mechanisms underlying the rhythmic bursts induced by NMDA microiontophoresis at the apical dendrites of CA1 pyramidal neurons. Hippocampus 13:150-163.

Bonansco C, Fuenzalida M (2016) Plasticity of Hippocampal Excitatory-Inhibitory Balance: Missing the Synaptic Control in the Epileptic Brain. Neural plasticity 2016:8607038.

Bonansco C, Gonzalez de la Vega A, Gonzalez Alegre P, Borde M, Garca-Segura LM, Buno W (2002) Tetanic stimulation of schaffer collaterals induces rhythmic bursts via NMDA receptor activation in rat CA1 pyramidal neurons. Hippocampus 12:434-446.

Borde M, Bonansco C, Buno W (1999) The activity-dependent potentiation of the slow Ca2+-activated K+ current regulates synaptic efficacy in rat CA1 pyramidal neurons. Pflugers Archiv : European journal of physiology 437:261-266.

Borde M, Cazalets JR, Buno W (1995) Activity-dependent response depression in rat hippocampal CA1 pyramidal neurons in vitro. Journal of neurophysiology 74:1714-1729.

Brickley SG, Mody I (2012) Extrasynaptic GABA(A) receptors: their function in the CNS and implications for disease. Neuron 73:23-34.

Buno W, Cabezas C, Fernandez de Sevilla D (2006) Presynaptic muscarinic control of glutamatergic synaptic transmission. Journal of molecular neuroscience : MN 30:161-164.

Buno W, Jr., Velluti JC (1977) Relationships of hippocampal theta cycles with bar pressing during self-stimulation. Physiology & behavior 19:615-621.

Burford NT, Tobin AB, Nahorski SR (1995) Differential coupling of m1, m2 and m3 muscarinic receptor subtypes to inositol 1,4,5-trisphosphate and adenosine 3',5'-cyclic monophosphate accumulation in Chinese hamster ovary cells. The Journal of pharmacology and experimental therapeutics 274:134-142.

Buzsaki G, Draguhn A (2004) Neuronal oscillations in cortical networks. Science 304:1926-1929.

Buzsaki G, Horvath Z, Urioste R, Hetke J, Wise K (1992) High-frequency network oscillation in the hippocampus. Science 256:1025-1027.

Buzsaki G, Wang XJ (2012) Mechanisms of gamma oscillations. Annual review of neuroscience 35:203-225.

Cabezas C, Buno W (2006) Distinct transmitter release properties determine differences in short-term plasticity at functional and silent synapses. Journal of neurophysiology 95:3024-3034.

Cabezas C, Buno W (2011) BDNF is required for the induction of a presynaptic component of the functional conversion of silent synapses. Hippocampus 21:374-385.

Cape EG, Manns ID, Alonso A, Beaudet A, Jones BE (2000) Neurotensin-induced bursting of cholinergic basal forebrain neurons promotes gamma and theta cortical activity together with waking and paradoxical sleep. The Journal of neuroscience : the official journal of the Society for Neuroscience 20:8452-8461.

Carcea I, Froemke RC (2013) Cortical plasticity, excitatory-inhibitory balance, and sensory perception. Progress in brain research 207:65-90.

Carrer HF, Araque A, Buno W (2003) Estradiol regulates the slow Ca2+-activated K+ current in hippocampal pyramidal neurons. The Journal of neuroscience : the official journal of the Society for Neuroscience 23:6338-6344.

Castillo PE, Chiu CQ, Carroll RC (2011) Long-term plasticity at inhibitory synapses. Current opinion in neurobiology 21:328-338.

Cohen AS, Abraham WC (1996) Facilitation of long-term potentiation by prior activation of metabotropic glutamate receptors. Journal of neurophysiology 76:953-962.

Costa-Mattioli M, Sossin WS, Klann E, Sonenberg N (2009) Translational control of long-lasting synaptic plasticity and memory. Neuron 61:10-26.

Chaves-Coira I, Martin-Cortecero J, Nunez A, Rodrigo-Angulo ML (2018) Basal Forebrain Nuclei Display Distinct Projecting Pathways and Functional Circuits to Sensory Primary and Prefrontal Cortices in the Rat. Frontiers in neuroanatomy 12:69.

Chen KC, Baxter MG, Rodefer JS (2004) Central blockade of muscarinic cholinergic receptors disrupts affective and attentional set-shifting. The European journal of neuroscience 20:1081-1088.

Chiu CQ, Barberis A, Higley MJ (2019) Preserving the balance: diverse forms of long-term GABAergic synaptic plasticity. Nature reviews Neuroscience 20:272-281.

de Kock CP, Sakmann B (2009) Spiking in primary somatosensory cortex during natural whisking in awake head-restrained rats is cell-type specific. Proceedings of the National Academy of Sciences of the United States of America 106:16446-16450.

Deneve S, Machens CK (2016) Efficient codes and balanced networks. Nature neuroscience 19:375-382.

Dennis SH, Pasqui F, Colvin EM, Sanger H, Mogg AJ, Felder CC, Broad LM, Fitzjohn SM, Isaac JT, Mellor JR (2016) Activation of Muscarinic M1 Acetylcholine Receptors Induces Long-Term Potentiation in the Hippocampus. Cerebral cortex 26:414-426.

Diez-Garcia A, Barros-Zulaica N, Nunez A, Buno W, Fernandez de Sevilla D (2017) Bidirectional Hebbian Plasticity Induced by Low-Frequency Stimulation in Basal Dendrites of Rat Barrel Cortex Layer 5 Pyramidal Neurons. Frontiers in cellular neuroscience 11:8.

Disney AA, Aoki C, Hawken MJ (2007) Gain modulation by nicotine in macaque v1. Neuron 56:701-713.

Dominguez S, Fernandez de Sevilla D, Buno W (2014) Postsynaptic activity reverses the sign of the acetylcholine-induced long-term plasticity of GABAA inhibition. Proceedings of the National Academy of Sciences of the United States of America 111:E2741-2750.

Dominguez S, Fernandez de Sevilla D, Buno W (2016) Muscarinic Long-Term Enhancement of Tonic and Phasic GABAA Inhibition in Rat CA1 Pyramidal Neurons. Frontiers in cellular neuroscience 10:244.

Dominguez S, Fernandez de Sevilla D, Buno W (2017) Acetylcholine Facilitates a Depolarization-Induced Enhancement of Inhibition in Rat CA1 Pyramidal Neurons. Cerebral cortex 27:852-862.

Dringenberg HC, Hamze B, Wilson A, Speechley W, Kuo MC (2007) Heterosynaptic facilitation of in vivo thalamocortical long-term potentiation in the adult rat visual cortex by acetylcholine. Cerebral cortex 17:839-848.

Dutar P, Nicoll RA (1988) Classification of muscarinic responses in hippocampus in terms of receptor subtypes and second-messenger systems: electrophysiological studies in vitro. The Journal of neuroscience : the official journal of the Society for Neuroscience 8:4214-4224.

Eggermann E, Feldmeyer D (2009) Cholinergic filtering in the recurrent excitatory microcircuit of cortical layer 4. Proceedings of the National Academy of Sciences of the United States of America 106:11753-11758.

Farrant M, Nusser Z (2005) Variations on an inhibitory theme: phasic and tonic activation of GABA(A) receptors. Nature reviews Neuroscience 6:215-229.

Feldmeyer D, Qi G, Emmenegger V, Staiger JF (2018) Inhibitory interneurons and their circuit motifs in the many layers of the barrel cortex. Neuroscience 368:132-151.

Fernandez de Sevilla D, Buno W (2003) Presynaptic inhibition of Schaffer collateral synapses by stimulation of hippocampal cholinergic afferent fibres. The European journal of neuroscience 17:555-558.

Fernandez de Sevilla D, Buno W (2010) The muscarinic long-term enhancement of NMDA and AMPA receptor-mediated transmission at Schaffer collateral synapses develop through different intracellular mechanisms. The Journal of neuroscience : the official journal of the Society for Neuroscience 30:11032-11042.

Fernandez de Sevilla D, Cabezas C, de Prada AN, Sanchez-Jimenez A, Buno W (2002) Selective muscarinic regulation of functional glutamatergic Schaffer collateral synapses in rat CA1 pyramidal neurons. The Journal of physiology 545:51-63.

Fernandez de Sevilla D, Nunez A, Borde M, Malinow R, Buno W (2008) Cholinergic-mediated IP3-receptor activation induces long-lasting synaptic enhancement in CA1 pyramidal neurons. The Journal of neuroscience : the official journal of the Society for Neuroscience 28:1469-1478.

Fisahn A, Yamada M, Duttaroy A, Gan JW, Deng CX, McBain CJ, Wess J (2002) Muscarinic induction of hippocampal gamma oscillations requires coupling of the M1 receptor to two mixed cation currents. Neuron 33:615-624.

Fries P, Nikolic D, Singer W (2007) The gamma cycle. Trends Neurosci 30:309-316.

Fries P, Reynolds JH, Rorie AE, Desimone R (2001) Modulation of oscillatory neuronal synchronization by selective visual attention. Science 291:1560-1563.

Froemke RC (2015) Plasticity of cortical excitatory-inhibitory balance. Annual review of neuroscience 38:195-219.

Gainey MA, Feldman DE (2017) Multiple shared mechanisms for homeostatic plasticity in rodent somatosensory and visual cortex. Philosophical transactions of the Royal Society of London Series B, Biological sciences 372.

Galvan EJ, Cosgrove KE, Barrionuevo G (2011) Multiple forms of long-term synaptic plasticity at hippocampal mossy fiber synapses on interneurons. Neuropharmacology 60:740-747.

Garcia-Munoz A, Barrio LC, Buno W (1993) Membrane potential oscillations in CA1 hippocampal pyramidal neurons in vitro: intrinsic rhythms and fluctuations entrained by sinusoidal injected current. Experimental brain research 97:325-333.

Gasparini S, Saviane C, Voronin LL, Cherubini E (2000) Silent synapses in the developing hippocampus: lack of functional AMPA receptors or low probability of glutamate release? Proceedings of the National Academy of Sciences of the United States of America 97:9741-9746.

Gaztelu JM, Buno W, Jr. (1982) Septo-hippocampal relationships during EEG theta rhythm. Electroencephalography and clinical neurophysiology 54:375-387.

Goldberg JH, Yuste R (2005) Space matters: local and global dendritic Ca2+ compartmentalization in cortical interneurons. Trends in neurosciences 28:158-167.

Golding NL, Staff NP, Spruston N (2002) Dendritic spikes as a mechanism for cooperative long-term potentiation. Nature 418:326-331.

Gu Z, Alexander GM, Dudek SM, Yakel JL (2017) Hippocampus and Entorhinal Cortex Recruit Cholinergic and NMDA Receptors Separately to Generate Hippocampal Theta Oscillations. Cell reports 21:3585-3595.

Haam J, Yakel JL (2017) Cholinergic modulation of the hippocampal region and memory function. Journal of neurochemistry 142 Suppl 2:111-121.

Hangya B, Borhegyi Z, Szilagyi N, Freund TF, Varga V (2009) GABAergic neurons of the medial septum lead the hippocampal network during theta activity. The Journal of neuroscience : the official journal of the Society for Neuroscience 29:8094-8102.

Hasselmo ME, Bower JM (1992) Cholinergic suppression specific to intrinsic not afferent fiber synapses in rat piriform (olfactory) cortex. Journal of neurophysiology 67:1222-1229.

Hasselmo ME, Giocomo LM (2006) Cholinergic modulation of cortical function. Journal of molecular neuroscience : MN 30:133-135.

Hasselmo ME, McGaughy J (2004) High acetylcholine levels set circuit dynamics for attention and encoding and low acetylcholine levels set dynamics for consolidation. Progress in brain research 145:207-231.

Hasselmo ME, Sarter M (2011) Modes and models of forebrain cholinergic neuromodulation of cognition. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 36:52-73.

Hausser M, Spruston N, Stuart GJ (2000) Diversity and dynamics of dendritic signaling. Science 290:739-744.

Hefft S, Jonas P (2005) Asynchronous GABA release generates long-lasting inhibition at a hippocampal interneuron-principal neuron synapse. Nature neuroscience 8:1319-1328.

Herrero JL, Roberts MJ, Delicato LS, Gieselmann MA, Dayan P, Thiele A (2008) Acetylcholine contributes through muscarinic receptors to attentional modulation in V1. Nature 454:1110-1114.

Himmelheber AM, Sarter M, Bruno JP (2000) Increases in cortical acetylcholine release during sustained attention performance in rats. Brain research Cognitive brain research 9:313-325.

Hounsgaard J (1978) Inhibition produced by iontophoretically applied acetylcholine in area CA1 of thin hippocampal slices from the rat. Acta physiologica Scandinavica 103:110-111.

Howe WM, Gritton HJ, Lusk NA, Roberts EA, Hetrick VL, Berke JD, Sarter M (2017) Acetylcholine Release in Prefrontal Cortex Promotes Gamma Oscillations and Theta-Gamma Coupling during Cue Detection. The Journal of neuroscience : the official journal of the Society for Neuroscience 37:3215-3230.

Huang CS, Shi SH, Ule J, Ruggiu M, Barker LA, Darnell RB, Jan YN, Jan LY (2005) Common molecular pathways mediate long-term potentiation of synaptic excitation and slow synaptic inhibition. Cell 123:105-118.

Humeau Y, Choquet D (2019) The next generation of approaches to investigate the link between synaptic plasticity and learning. Nature neuroscience 22:1536-1543.

Ishii M, Kurachi Y (2006) Muscarinic acetylcholine receptors. Current pharmaceutical design 12:3573-3581.

Ji W, Suga N (2003) Development of reorganization of the auditory cortex caused by fear conditioning: effect of atropine. Journal of neurophysiology 90:1904-1909.

Jimenez-Capdeville ME, Dykes RW (1996) Changes in cortical acetylcholine release in the rat during day and night: differences between motor and sensory areas. Neuroscience 71:567-579.

Kowalski J, Gan J, Jonas P, Pernia-Andrade AJ (2016) Intrinsic membrane properties determine hippocampal differential firing pattern in vivo in anesthetized rats. Hippocampus 26:668-682.

Levey AI, Kitt CA, Simonds WF, Price DL, Brann MR (1991) Identification and localization of muscarinic acetylcholine receptor proteins in brain with subtype-specific antibodies. The Journal of neuroscience : the official journal of the Society for Neuroscience 11:3218-3226.

Li G, Bien-Ly N, Andrews-Zwilling Y, Xu Q, Bernardo A, Ring K, Halabisky B, Deng C, Mahley RW, Huang Y (2009) GABAergic interneuron dysfunction impairs hippocampal neurogenesis in adult apolipoprotein E4 knockin mice. Cell stem cell 5:634-645.

Liao D, Hessler NA, Malinow R (1995) Activation of postsynaptically silent synapses during pairing-induced LTP in CA1 region of hippocampal slice. Nature 375:400-404.

Lisman JE, Jensen O (2013) The theta-gamma neural code. Neuron 77:1002-1016.
Mahajan G, Nadkarni S (2019) Intracellular calcium stores mediate metaplasticity at hippocampal dendritic spines. The Journal of physiology 597:3473-3502.
Marder CP, Buonomano DV (2004) Timing and balance of inhibition enhance the effect of long-term potentiation on cell firing. The Journal of neuroscience : the official journal of the Society for Neuroscience 24:8873-8884.
McBain CJ, Kauer JA (2009) Presynaptic plasticity: targeted control of inhibitory networks. Current opinion in neurobiology 19:254-262.
McCormick DA, Prince DA (1986) Mechanisms of action of acetylcholine in the guinea-pig cerebral cortex in vitro. The Journal of physiology 375:169-194.
Metherate R, Tremblay N, Dykes RW (1988) Transient and prolonged effects of acetylcholine on responsiveness of cat somatosensory cortical neurons. Journal of neurophysiology 59:1253-1276.
Misgeld U, Bijak M, Jarolimek W (1995) A physiological role for GABAB receptors and the effects of baclofen in the mammalian central nervous system. Progress in neurobiology 46:423-462.
Monday HR, Younts TJ, Castillo PE (2018) Long-Term Plasticity of Neurotransmitter Release: Emerging Mechanisms and Contributions to Brain Function and Disease. Annual review of neuroscience 41:299-322.
Nabavi S, Fox R, Proulx CD, Lin JY, Tsien RY, Malinow R (2014) Engineering a memory with LTD and LTP. Nature 511:348-352.
Navarrete M, Perea G, Fernandez de Sevilla D, Gomez-Gonzalo M, Nunez A, Martin ED, Araque A (2012) Astrocytes mediate in vivo cholinergic-induced synaptic plasticity. PLoS biology 10:e1001259.
Nunez A, Dominguez S, Buno W, Fernandez de Sevilla D (2012) Cholinergic-mediated response enhancement in barrel cortex layer V pyramidal neurons. Journal of neurophysiology 108:1656-1668.
Nunez A, Garcia-Austt E, Buno W (1990) Slow intrinsic spikes recorded in vivo in rat CA1-CA3 hippocampal pyramidal neurons. Experimental neurology 109:294-299.
Nunez A, Garcia-Austt E, Buno W, Jr. (1987) Intracellular theta-rhythm generation in identified hippocampal pyramids. Brain research 416:289-300.
Obermayer J, Verhoog MB, Luchicchi A, Mansvelder HD (2017) Cholinergic Modulation of Cortical Microcircuits Is Layer-Specific: Evidence from Rodent, Monkey and Human Brain. Frontiers in neural circuits 11:100.
Oldford E, Castro-Alamancos MA (2003) Input-specific effects of acetylcholine on sensory and intracortical evoked responses in the "barrel cortex" in vivo. Neuroscience 117:769-778.
Pelkey KA, Chittajallu R, Craig MT, Tricoire L, Wester JC, McBain CJ (2017) Hippocampal GABAergic Inhibitory Interneurons. Physiological reviews 97:1619-1747.
Poser S, Storm DR (2001) Role of Ca2+-stimulated adenylyl cyclases in LTP and memory formation. International journal of developmental neuroscience : the official journal of the International Society for Developmental Neuroscience 19:387-394.
Power JM, Oh MM, Disterhoft JF (2001) Metrifonate decreases sI(AHP) in CA1 pyramidal neurons in vitro. Journal of neurophysiology 85:319-322.
Power JM, Sah P (2008) Competition between calcium-activated K+ channels determines cholinergic action on firing properties of basolateral amygdala

projection neurons. The Journal of neuroscience : the official journal of the Society for Neuroscience 28:3209-3220.

Qian J, Saggau P (1997) Presynaptic inhibition of synaptic transmission in the rat hippocampus by activation of muscarinic receptors: involvement of presynaptic calcium influx. British journal of pharmacology 122:511-519.

Radnikow G, Feldmeyer D (2018) Layer- and Cell Type-Specific Modulation of Excitatory Neuronal Activity in the Neocortex. Frontiers in neuroanatomy 12:1.

Rigas P, Castro-Alamancos MA (2009) Impact of persistent cortical activity (up States) on intracortical and thalamocortical synaptic inputs. Journal of neurophysiology 102:119-131.

Rivera C, Voipio J, Thomas-Crusells J, Li H, Emri Z, Sipila S, Payne JA, Minichiello L, Saarma M, Kaila K (2004) Mechanism of activity-dependent downregulation of the neuron-specific K-Cl cotransporter KCC2. The Journal of neuroscience : the official journal of the Society for Neuroscience 24:4683-4691.

Rodriguez R, Kallenbach U, Singer W, Munk MH (2004) Short- and long-term effects of cholinergic modulation on gamma oscillations and response synchronization in the visual cortex. The Journal of neuroscience : the official journal of the Society for Neuroscience 24:10369-10378.

Rose CR, Konnerth A (2001) Stores not just for storage. intracellular calcium release and synaptic plasticity. Neuron 31:519-522.

Sanchez-Vives MV, McCormick DA (2000) Cellular and network mechanisms of rhythmic recurrent activity in neocortex. Nature neuroscience 3:1027-1034.

Savanthrapadian S, Meyer T, Elgueta C, Booker SA, Vida I, Bartos M (2014) Synaptic properties of SOM- and CCK-expressing cells in dentate gyrus interneuron networks. The Journal of neuroscience : the official journal of the Society for Neuroscience 34:8197-8209.

Scarr E, Seo MS, Aumann TD, Chana G, Everall IP, Dean B (2016) The distribution of muscarinic M1 receptors in the human hippocampus. Journal of chemical neuroanatomy 77:187-192.

Schiller J, Schiller Y (2001) NMDA receptor-mediated dendritic spikes and coincident signal amplification. Current opinion in neurobiology 11:343-348.

Serwanski DR, Miralles CP, Christie SB, Mehta AK, Li X, De Blas AL (2006) Synaptic and nonsynaptic localization of GABAA receptors containing the alpha5 subunit in the rat brain. The Journal of comparative neurology 499:458-470.

Shu Y, Hasenstaub A, McCormick DA (2003) Turning on and off recurrent balanced cortical activity. Nature 423:288-293.

Singer W (1999) Neuronal synchrony: a versatile code for the definition of relations? Neuron 24:49-65, 111-125.

Soma S, Shimegi S, Suematsu N, Sato H (2013) Cholinergic modulation of response gain in the rat primary visual cortex. Scientific reports 3:1138.

Spencer JP, Middleton LJ, Davies CH (2010) Investigation into the efficacy of the acetylcholinesterase inhibitor, donepezil, and novel procognitive agents to induce gamma oscillations in rat hippocampal slices. Neuropharmacology 59:437-443.

Stoiljkovic M, Kelley C, Nagy D, Leventhal L, Hajos M (2016) Selective activation of alpha7 nicotinic acetylcholine receptors augments hippocampal oscillations. Neuropharmacology 110:102-108.

Teles-Grilo Ruivo LM, Baker KL, Conway MW, Kinsley PJ, Gilmour G, Phillips KG, Isaac JTR, Lowry JP, Mellor JR (2017) Coordinated Acetylcholine Release in

Prefrontal Cortex and Hippocampus Is Associated with Arousal and Reward on Distinct Timescales. Cell reports 18:905-917.

Teles-Grilo Ruivo LM, Mellor JR (2013) Cholinergic modulation of hippocampal network function. Frontiers in synaptic neuroscience 5:2.

Tremblay R, Lee S, Rudy B (2016) GABAergic Interneurons in the Neocortex: From Cellular Properties to Circuits. Neuron 91:260-292.

Turrigiano G (2012) Homeostatic synaptic plasticity: local and global mechanisms for stabilizing neuronal function. Cold Spring Harbor perspectives in biology 4:a005736.

Vanderheyden P, Gies JP, Ebinger G, De Keyser J, Landry Y, Vauquelin G (1990) Human M1-, M2- and M3-muscarinic cholinergic receptors: binding characteristics of agonists and antagonists. Journal of the neurological sciences 97:67-80.

Vertes RP (2005) Hippocampal theta rhythm: a tag for short-term memory. Hippocampus 15:923-935.

Womelsdorf T, Fries P, Mitra PP, Desimone R (2006) Gamma-band synchronization in visual cortex predicts speed of change detection. Nature 439:733-736.

Woodin MA, Ganguly K, Poo MM (2003) Coincident pre- and postsynaptic activity modifies GABAergic synapses by postsynaptic changes in Cl- transporter activity. Neuron 39:807-820.

Yan J, Zhang Y (2005) Sound-guided shaping of the receptive field in the mouse auditory cortex by basal forebrain activation. The European journal of neuroscience 21:563-576.

Zhang H, Lin SC, Nicolelis MA (2010) Spatiotemporal coupling between hippocampal acetylcholine release and theta oscillations in vivo. The Journal of neuroscience : the official journal of the Society for Neuroscience 30:13431-13440.

Zhou S, Yu Y (2018) Synaptic E-I Balance Underlies Efficient Neural Coding. Frontiers in neuroscience 12:46.

Figure 1

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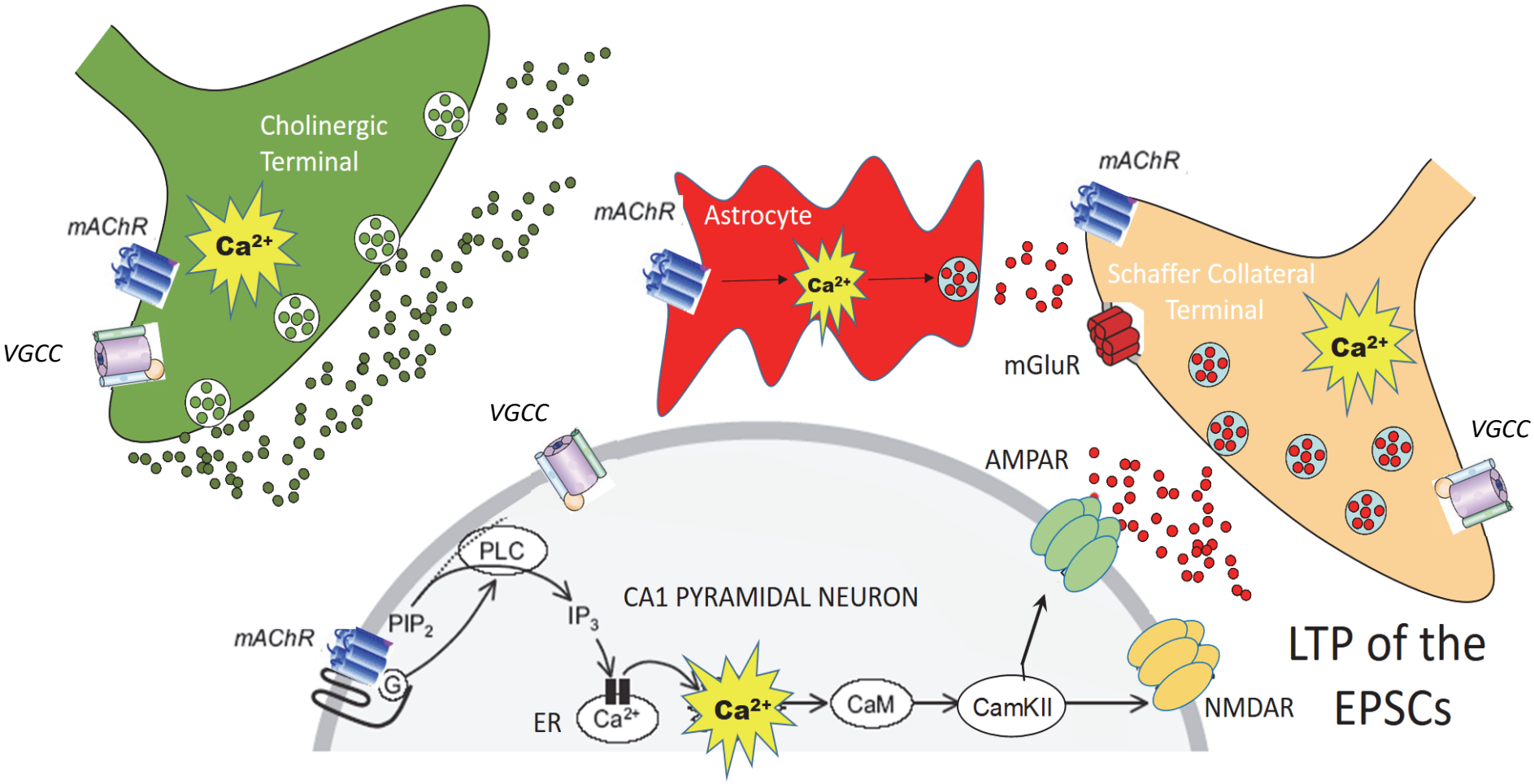

Figure 2

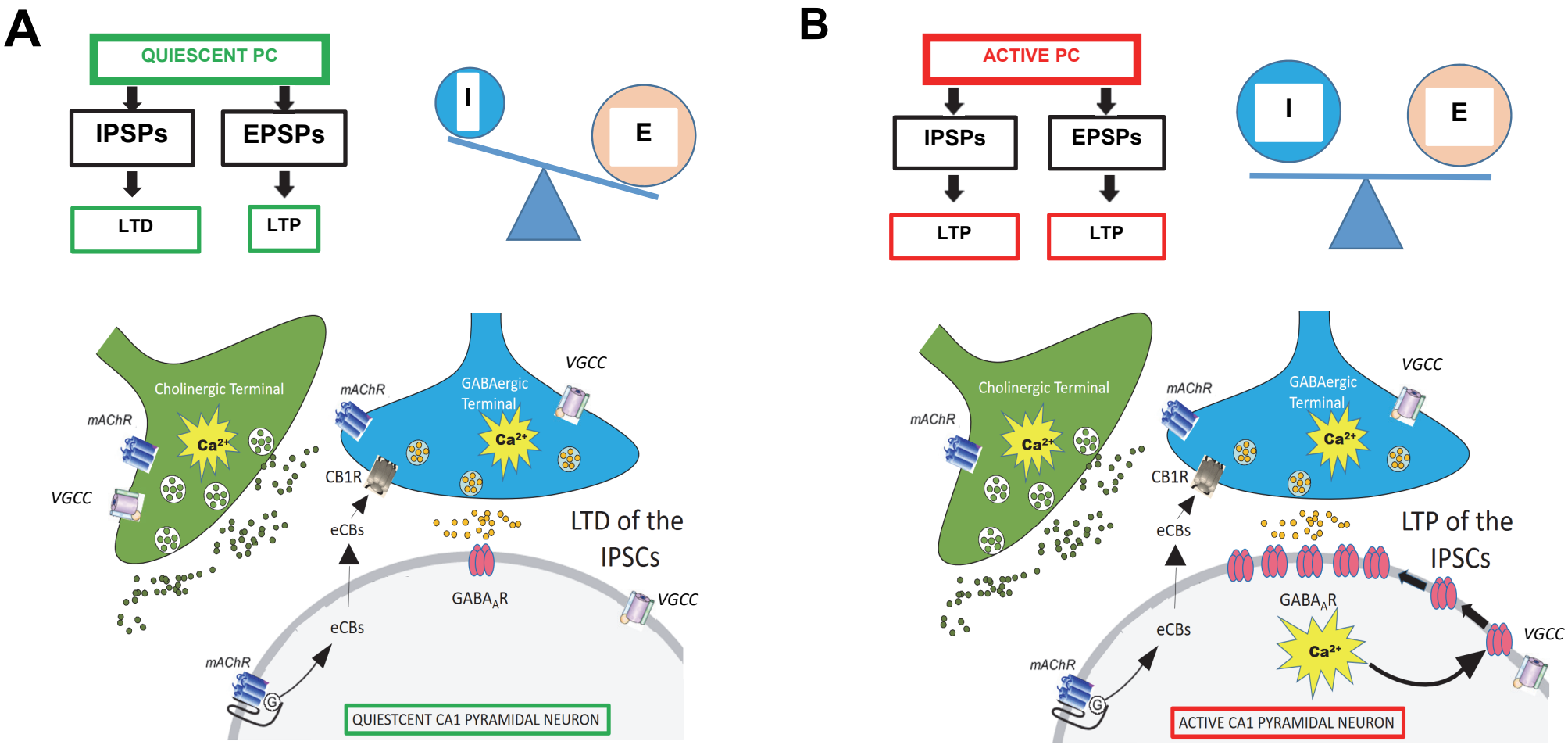

Figure 3

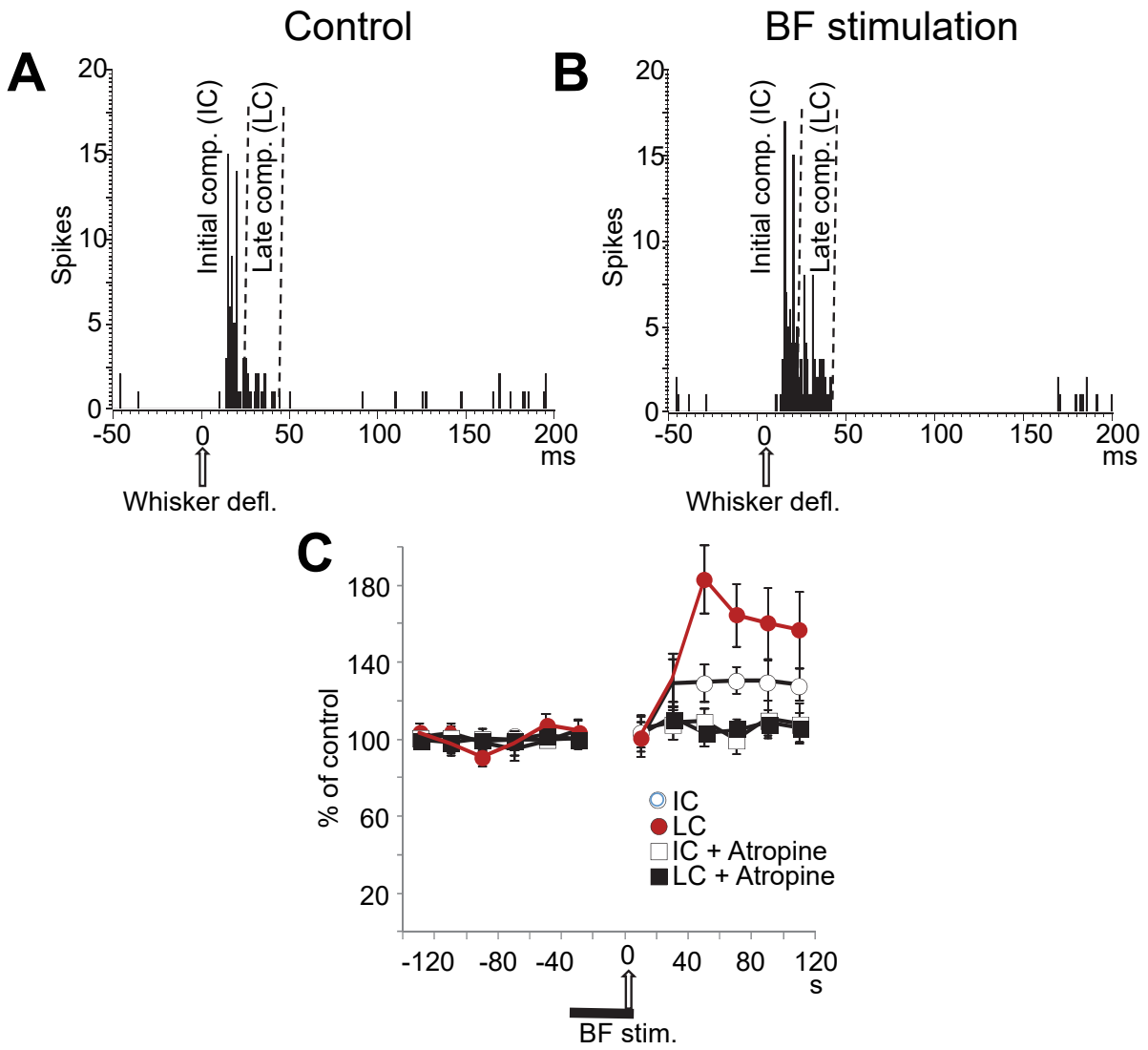

FIGURE LEGENDS

Figure 1. mAChR activation induces cholinergic LTP at Schaffer collateral-CA1 pyramidal neuron synapses. Schematic representation of cholinergic, SC terminals, a CA1 pyramidal neuron and astrocyte. mAChR (blue) activation induces Ca^{2+} elevations *via* release from the ER and influx through VGCC. The LTP is expressed postsynaptically by an increased AMPAR (green) and NMDAR (orange) response, and presynaptically *via* an increased glutamate release probability.

Figure 2. mAChR activation induces cholinergic LTD or LTP at inhibitory synapses depending on the activity of the postsynaptic CA1 pyramidal neuron. **A, top left.** LTD of IPSP and LTP of EPSP are induced by mAChR activation when the postsynaptic neuron is quiescent. **A, top right**. With a quiescent postsynaptic neuron there is an unbalance favoring excitation (E) versus inhibition (I). **A, bottom.** With a quiescent postsynaptic neuron mAChR activation favors eCB release that via activation of presynaptic CB_1Rs induces a long lasting decrease in GABA release probability. **B, top**. With an active postsynaptic neuron mAChR activation induces LTP of EPSPs and IPSPs, balancing excitation (E) and inhibition (I). **B, bottom**. With an active postsynaptic neuron the increased Ca^{2+} *via* release from the ER and influx through VGCC induces LTP of EPSPs (as in **A, bottom**) and LTP of IPSCs by increasing $GABA_A$R expression.

Figure 3. Basal forebrain stimulation induces a long-term cholinergic-mediated enhancement of whisker responses in the anesthetized rat barrel cortex. A. Control PSTH showing initial (IC) and late (LC) response components induced by whisker deflection (arrow). **B.** PSTH following basal forebrain stimulation, note the increased late component. **C.** Number of spikes in IC and LC versus time, before and

following basal forebrain stimulation (arrow), in the control and after atropine injection.