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TOPICAL REVIEW

Regulation of hippocampal inhibitory circuits by nicotinic acetylcholine receptors

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Abstract The hippocampal network comprises a large variety of locally connected GABAergic interneurons exerting a powerful control on network excitability and which are responsible for the oscillatory behaviour crucial for information processing. GABAergic interneurons receive an important cholinergic innervation from the medial septum-diagonal band complex of the basal forebrain and are endowed with a variety of muscarinic and nicotinic acetylcholine receptors (mAChRs and nAChRs) that regulate their activity. Deficits in the cholinergic system lead to the impairment of high cognitive functions, which are particularly relevant in neurodegenerative pathologies such as Alzheimer's and Parkinson's diseases as well as in schizophrenia. Here, we highlight some recent advances in the mechanisms by which cholinergic signalling via nAChRs regulates local inhibitory circuits in the hippocampus, early in postnatal life and in adulthood. We also discuss recent findings concerning the functional role of nAChRs in controlling short- and long-term modifications of synaptic efficacy. Insights into these processes may provide new targets for the therapeutic control of pathological conditions associated with cholinergic dysfunctions.

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Abbreviations ACh, acetylcholine; α-BGTx, alpha-bungarotoxin; DHβE, dihydro-beta-eritroidine; GDP, giant depolarizing potential; HFS, high-frequency stimulation; LTD, long-term depression; LTP, long-term potentiation; mAChR, muscarinic acetylcholine receptor; MAPK, mitogen-activated protein kinase; MLA, methyllycaconitine; nAChR, nicotinic acetylcholine receptor; O-LM, oriens-lacunosum moleculare; STP, short-term potentiation.

Introduction

Since the pioneering studies of Ramón y Cajal (1899) and Lorente de Nó (1922) it has become clear that local circuit inhibitory interneurons constitute a very heterogeneous group of cells. By releasing γ-aminobutyric acid (GABA) into their postsynaptic targets they exert a powerful control on network excitability and are responsible for the oscillatory behaviour, crucial for information processing in the brain. Interneurons can be differentially classified according to their morphology, biophysical properties, molecular expression profile and connectivity (Freund & Buzsaki, 1996; McBain & Fisahn, 2001). In the

Enrico Cherubini (right) is Full Professor at SISSA, Trieste. He earned his MD and specialized in child neurology at the University of Rome. After being trained with H. Gastaut (Marseille), N. Buchwald (UCLA) and R. A. North (MIT) he moved to Paris where he was appointed 'Directeur de Recherche' at the INSERM unit directed by Y. Ben-Ari. His research interest focuses mainly on the molecular and cellular mechanisms regulating synaptic plasticity processes in the developing hippocampus including those mediated by nicotinic acetylcholine receptor (nAChR) signalling. **Marilena Griguoli** (left) obtained her PhD from SISSA, studying the effects of nAChRs on oriens-lacunosum moleculare interneurons in the hippocampus. As a post-doc she joined the group of C. Mulle in Bordeaux.

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CA1 hippocampal region for instance, relatively uniform excitatory pyramidal cells are supported by more than 20 different types of interneurons (Klausberger & Somogyi, 2008).

In contrast to principal cells that exhibit long axons projecting information to distant brain areas, GABAergic interneurons present short axons that selectively innervate different domains of pyramidal cells, thus providing the main source of feedback and feed-forward inhibition (Miles *et al.* 1996; Maccaferri & Lacaille, 2003; Kullmann, 2011). The spatio-temporal dynamics between the activity of interneurons and pyramidal cells leads to coherent oscillations (Klausberger *et al.* 2003, 2004; Somogyi & Klausberger, 2005), which support different behavioural states and high cognitive tasks (Klausberger & Somogyi, 2008). Oscillatory rhythms are facilitated by the intrinsic properties of GABA-releasing cells (Maccaferri & McBain, 1996) and by their electrical coupling via gap junctions (Hestrin & Galarreta, 2005).

Interestingly hippocampal interneurons receive an important cholinergic innervation from the medial septum–diagonal band complex of the basal forebrain (Frotscher & Léránth, 1985) and are endowed with nicotinic acetylcholine receptors (nAChRs), the activation of which contributes to the setting of the cooperative temporal framework that provides the basis for high cognitive functions (Rezvani & Levin, 2001).

Neuronal nAChRs belong to the large cysteine loop of the ligand-gated ion channel superfamily and are composed of five subunits organized in a variety of allosteric oligomers (Changeux & Edelstein, 2005). Several different nAChR subunits, $\alpha 2$–$\alpha 10$ and $\beta 2-\beta 4$, have been cloned. They may assemble in various combinations to generate a large variety of nAChR subtypes with different biophysical and pharmacological properties (Le Novère & Changeux, 1995). While $\alpha 7-\alpha 10$ subunits form channels sensitive to the snake venom α-bungarotoxin (α-BGTx), $\alpha 2$ and $\alpha 6$ combine with $\beta 2-\beta 4$ subunits to produce channels insensitive to α-BGTx. The two major nAChR subtypes present in the hippocampus are homomeric $\alpha 7$ and heteromeric $\alpha 4\beta 2$ nAChRs (Alkondon & Albuquerque, 2004). These receptors are permeable to cations including calcium. Calcium permeability varies among different receptor types, being highest in the homomeric $\alpha 7$ nAChRs (Fucile, 2004). This characteristic allows nAChRs to play a key role in calcium-mediated events including neurotransmitter release, regulation of a variety of signal transduction cascades, cell survival and apoptosis.

Deficits in the cholinergic system produce impairment of cognitive functions, which are particularly relevant during senescence and in age-related neurodegenerative pathologies (Selkoe, 2002), and nicotine is known to enhance cognitive functions, via nAChRs, in some Alzheimer's disease patients (Nordberg, 1994).

This review examines how cholinergic signalling controls via nAChRs the correlated network activity present in the hippocampus early in postnatal life and orchestrates the functional properties of GABAergic interneurons in a cell-specific manner. In particular, recent advances in nAChR-mediated modulation of short- and long-term synaptic plasticity processes in local inhibitory circuits are highlighted.

nAChRs control correlated network activity in the immature hippocampus

It has been well established that nAChRs contribute to the functional maturation of the brain (Chang & Berg, 1999; Aramakis *et al.* 2000; Rossi *et al.* 2001; Kawa, 2002) and that their excessive activation by perinatal exposure to nicotine impairs cognitive functions by interfering with the development of areas involved in these processes (Johns *et al.* 1982; Levin *et al.* 1993; Ernst *et al.* 2001; Linnet *et al.* 2003).

In the rat hippocampus, mRNAs for the $\alpha 7$ and $\beta 2$ subunits are present early during embryogenesis but their expression patterns differ. The density of [^{3}H]-epibatidine binding sites, an indicator of heteromeric nAChRs, remains stable during postnatal development (Tribollet *et al.* 2004). Conversely, the expression of $\alpha 7$ mRNA and the density of [^{125}I]-α-BGTx binding sites, an indicator of $\alpha 7$ nAChRs, are particularly high during the first postnatal week and decrease subsequently (Shacka & Robinson, 1998; Tribollet *et al.* 2004). This suggests that, at least in the CA1 region of the hippocampus, the balance between $\alpha 7$- and $\beta 2$-containing nAChRs changes during postnatal development. This may lead to differences in nicotine-induced modulation of synaptic and network activity.

At the network level, the immature hippocampus is characterized by a correlated activity (giant depolarizing potentials or GDPs; Ben-Ari *et al.* 1989), generated by the synergistic action of glutamate and GABA which, at this developmental stage, is depolarizing and excitatory (Cherubini *et al.* 1991; Ben-Ari *et al.* 2007). This activity represents a primordial form of synchrony between neurons preceding more organized forms such as the theta and the gamma rhythms and it is instrumental in enhancing synaptic efficacy at poorly developed GABAergic and glutamatergic synapses (Kasyanov *et al.* 2004; Mohajerani *et al.* 2007). A previous report on CA3 pyramidal neurons in the hippocampus has demonstrated that nAChRs are present and functional from the first postnatal day and that nicotine cholinergic signalling via $\alpha 7$ and non-$\alpha 7$ nAChRs exerts a powerful regulatory action on network-driven GDPs (Maggi *et al.* 2001). Since glutamatergic terminals projecting to pyramidal neurons are controlled only by $\alpha 7$ nAChRs, the nicotine-induced

increase in GDP frequency observed in $\alpha7^{-/-}$ mice can be attributed to the enhancement of GABA release from GABAergic interneurons via $\beta2$-containing nAChRs (Le Magueresse *et al.* 2006; Fig. 1). It is worth noting that, in $\alpha7^{-/-}$ mice, nicotine failed to increase the frequency of interictal discharges obtained towards the end of the first postnatal week by blocking the $GABA_A$ receptor with bicuculline (Le Magueresse *et al.* 2006). Activation of $\alpha7$ nAChRs, probably localized on associative-commissural fibres involved in the generation of bursting activity (Miles & Wong, 1987), may account for this effect. Therefore, while modulation of glutamatergic signalling needs the activation of $\alpha7$ nAChRs (see also Maggi *et al.* 2003), regulation of GABAergic transmission needs the activation of both $\alpha7$- and $\beta2$-containing nAChRs (Le Magueresse *et al.* 2006).

In addition, at least in the CA1 region of the hippocampus, the potency of the observed effects and the involved nAChR subtypes vary among different lamina in a neuron-type-specific way (Le Magueresse *et al.* 2006). This may differently affect the fine regional tuning of GABAergic and glutamatergic transmission and hippocampal wiring. It is important to mention that during the first week of postnatal life nicotinic cholinergic

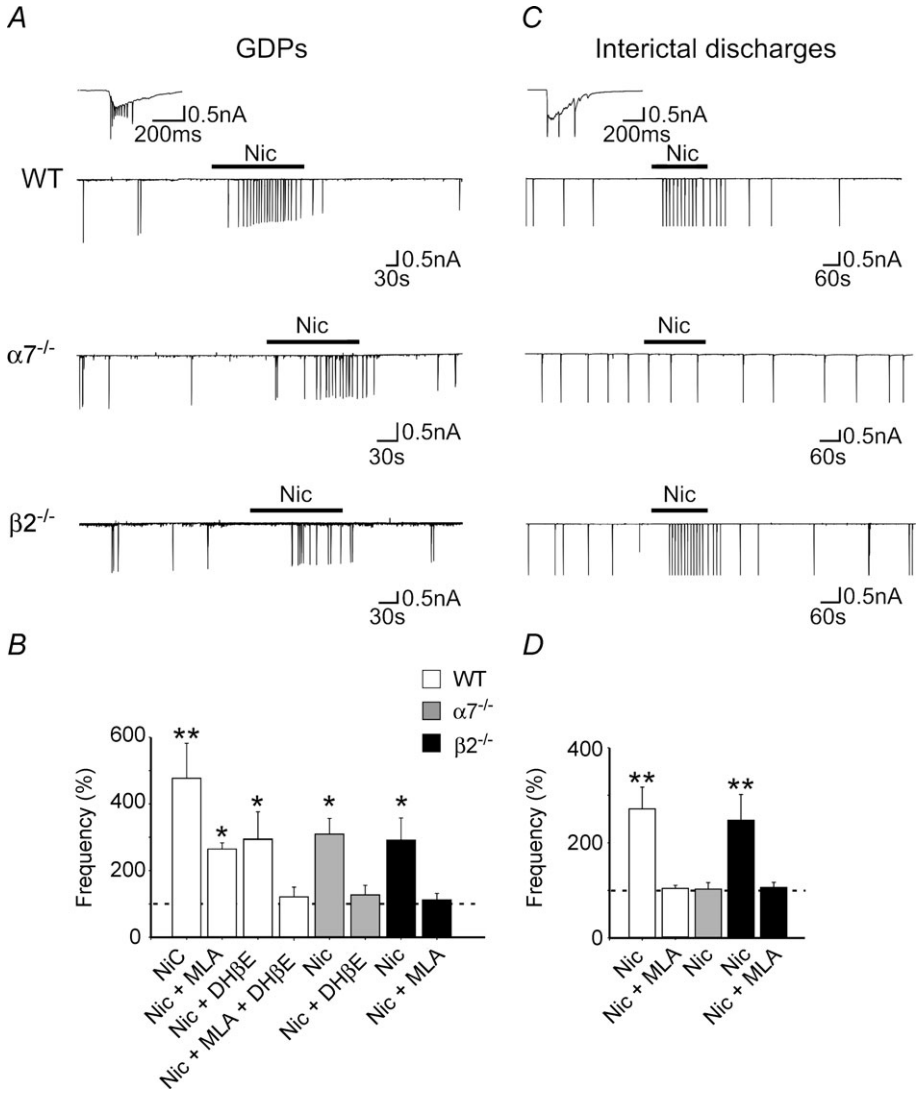

Figure 1. Different regulation of GDPs and interictal discharges by nAChRs
A, representative traces recorded at P5–P6 from CA1 pyramidal neurons in hippocampal slices obtained from WT, $\alpha7^{-/-}$ and $\beta2^{-/-}$ mice, respectively, in control conditions and in the presence of nicotine (1 μM). The inset above the traces represents a GDP at an expanded time scale. *B*, each column represents nicotine-induced changes of GDP frequency as a percentage of control (dashed line); $n = 6$–12. *C* and *D*, as in *A* and *B* but for interictal discharges induced by bicuculline at P9–P10 (see the inset above the traces); $n = 3$–13; $^*P < 0.05$; $^{**}P < 0.01$. While nicotine enhanced GDPs frequency via activation of $\alpha7$- and $\beta2$-containing nAChRs, it increased the frequency of interictal discharges only via $\alpha7$ nAChRs, indicating a different distribution of nAChRs between GABAergic interneurons and principal cells. Modified from Le Magueresse *et al.* 2006.

activity drives, mainly via α7 nAChRs, maturation of GABAergic signalling, contributing in this way to the shift of GABA from the depolarizing to the hyperpolarizing direction (Liu *et al.* 2006).

nAChRs regulate the functional properties of GABAergic interneurons in a cell-specific manner

In the rat and mouse hippocampus, nAChRs are expressed at both pre- and post-synaptic sites (Zoli *et al.* 1998; Sudweeks & Yakel, 2000; Fabian-Fine *et al.* 2001). The activation of presynaptic nAChRs induces a calcium-dependent increase in the probability of transmitter release (Gray *et al.* 1996; Vizi & Lendvai, 1999; Alkondon & Albuquerque, 2001). In particular, α7 nAChRs that are expressed on both glutamatergic and GABAergic terminals modulate the release of both glutamate and GABA. Calcium increase in presynaptic nerve terminals occurs through nAChR channels, high voltage-dependent calcium channels (of the N, P/Q and R types) activated by the depolarizing action of nicotine or endogenously released ACh and calcium-induced calcium release from internal stores (Le Magueresse & Cherubini, 2007). Interestingly, activation of $\alpha3\beta4$ nAChRs localized on axon terminals of parvalbumin-positive cells can boost tetrodotoxin-insensitive GABA release via low voltage-gated calcium channels (of the T-type) and calcium-induced calcium release (Tang *et al.* 2011). The cholinergic enhancement of GABA release from perisomatic-targeting parvalbumin-expressing cells may affect gamma oscillations which, together with theta waves, occur during spatial navigation, memory tasks and rapid-eye-movement sleep (Klausberger & Somogyi, 2008). Furthermore, $\alpha3\beta4\beta2$ nAChRs, present on glutamatergic axons synapsing on stratum radiatum interneurons, exert a powerful control on their resting excitability (Alkondon *et al.* 2011). Thus, mecamylamine (a non selective nAChRs antagonist) is able to reduce the frequency of action currents recorded in cell-attached mode from basket cells in stratum radiatum. The lack of methyllycaconitine (MLA; a selective α7 nAChR antagonist) in the modification of the firing frequency of stratum radiatum interneurons may be attributed to the low level of 'ambient' acetylcholine (ACh) in hippocampal slices, insufficient to trigger interneuronal firing via low-affinity α7 nAChRs, apparently localized together with $\alpha3\beta4\beta2$ on glutamatergic axons.

The activation of nAChRs localized postsynaptically on the somato-dendritic compartments produces specific responses in pyramidal cells and interneurons. However, while in pyramidal cells nAChR agonists produce no responses or barely detectable responses (Frazier *et al.* 1998*b*; McQuiston & Madison, 1999; Khiroug *et al.* 2003; but see Ji *et al.* 2001), in interneurons they induce responses whose kinetics and pharmacology vary among different cell types (Frazier *et al.* 1998*a*). Previous studies, using conventional pharmacological tools, have indicated that a local application of ACh to interneurons present in stratum radiatum and stratum lacunosum moleculare induces fast and slow decaying responses selectively blocked by α-BGTx/MLA or DHβE, indicating that they are mediated by α7 and β2 containing nAChRs, respectively (Frazier *et al.* 1998*a*, Alkondon *et al.* 1999). It is worth noting that α7 nAChRs undergo rapid desensitization (Hogg *et al.* 2003), a condition that would limit, in case of excessive agonist stimulation, membrane excitability and action potential firing (Alkondon *et al.* 2000). Fast and slow responses to ACh can be also recorded in stratum oriens interneurons (McQuiston & Madison, 1999). These cells are innervated by axon collaterals of pyramidal cells (Blasco-Ibanez & Freund, 1995) and project back to principal cells in stratum lacunosum moleculare (Lacaille *et al.* 1987; Ali & Thompson, 1998; Maccaferri *et al.* 2000; Maccaferri, 2005), contributing in this way to local feedback circuits. The kinetics correlation of currents evoked by ACh in stratum radiatum and stratum oriens interneurons with single-cell RT-PCR analysis revealed responses with fast kinetics, mediated by α3 and α7 subunits and responses with slow kinetics mediated by α2 and α4 subunits (Sudweeks & Yakel, 2000). The α4 and α2 subunits, certainly in combination with one or more β subunits, may be the major contributors to slow activating non-α7 responses detected in stratum radiatum and stratum oriens interneurons. In particular, stratum oriens interneurons express high levels of α2 subunits (Wada *et al.* 1989; Yakel & Shao, 2004), which support sustained non-desensitizing responses (Jia *et al.* 2009). According to McQuiston & Madison (1999), interneurons localized near the stratum pyramidale with axons providing perisomatic inhibition are insensitive to nAChR agonists. A schematic simplified view of different subtypes of nAChRs expressed on pyramidal cells and GABAergic interneurons of the CA1 hippocampal region is represented in Fig. 2.

nAChRs can be endogenously activated by acetylcholine released from the septal cholinergic projection (Frotscher & Léránth, 1985) or from intrinsic cholinergic interneurons (Frotscher *et al.* 1986). The latter comprise a small number of cells localized in the dentate gyrus and in the hippocampus proper, immunopositive for the acetylcholine-synthesizing enzyme choline acetyltransferase (Frotscher *et al.* 2000) and projecting specifically to GABAergic interneurons (Freund & Buzsaki, 1996). ACh released from cholinergic interneurons would regulate, via nAChRs present on GABAergic cells, network activity generated in the rat and mouse CA3 hippocampal region (Cobb *et al.* 1999). Thus, after degeneration of septal cholinergic terminals, the hippocampal network is still able to support

nAChR-dependent theta-mode activity, suggesting that intrinsic cholinergic circuits may provide the neurotransmitter necessary for nAChR activation (Cobb *et al.* 1999).

It is important to mention that cholinergic fibres arising from the medial septum–diagonal band complex have a number of transmitter-containing varicosities which only in a few cases face postsynaptic specializations (Descarries *et al.* 2004). This has led to the idea that cholinergic signalling may occur mainly via non-synaptic volume transmission (Umbriaco *et al.* 1995). In the volume transmission mode, ACh released from the synaptic cleft and/or from non-synaptic varicosities diffuses away to activate extrasynaptic nAChRs. This may explain the higher probability of producing slow nAChRs-mediated responses upon sustained stimulation of cholinergic fibres (Ren *et al.* 2011).

Fast cholinergic synaptic signalling involving vesicle exocytosis has been clearly detected in interneurons, while its presence in principal cells has been questioned (but see Hefft *et al.* 1999 and Grybko *et al.* 2011, for fast nAChR-mediated EPSCs in rats and mice, respectively). Hence, electrical stimulation of cholinergic fibres, in the presence of blockers of ionotropic glutamatergic and GABAergic transmission, elicits in stratum radiatum interneurons fast α7-mediated synaptic responses (Alkondon *et al.* 1998; Frazier *et al.* 1998*b*, 2003).

It is clear from this overview that nAChRs enhance GABAergic transmission from hippocampal interneurons. The magnitude and the final output of the response would depend on the subtypes of receptors involved and on neuronal connectivity. This may inhibit or disinhibit principal cells (Ji & Dani, 2000). Disinhibition of pyramidal neurons has been shown to facilitate gamma oscillations (Wang & Buzsaki, 1996).

nAChRs regulate the activity of O-LM interneurons

O-LM interneurons constitute a well-defined cellular population with soma and horizontal dendrites running parallel to the alveus and long axons that target the apical dendritic tufts of CA1 pyramidal cells aligned with entorhinal cortical inputs in stratum lacunosum moleculare (Lacaille *et al.* 1987; Maccaferri & McBain, 1996; Ali & Thomson, 1998; Maccaferri *et al.* 2000). O-LM interneurons, which contain somatostatin and express mGluR1α and neuropeptide Y receptors (Baude *et al.* 1993; Freund & Buzsaki, 1996; Katona *et al.* 1999; Maccaferri *et al.* 2000; Losonczy *et al.* 2002), exhibit fast spiking firing patterns caused by high

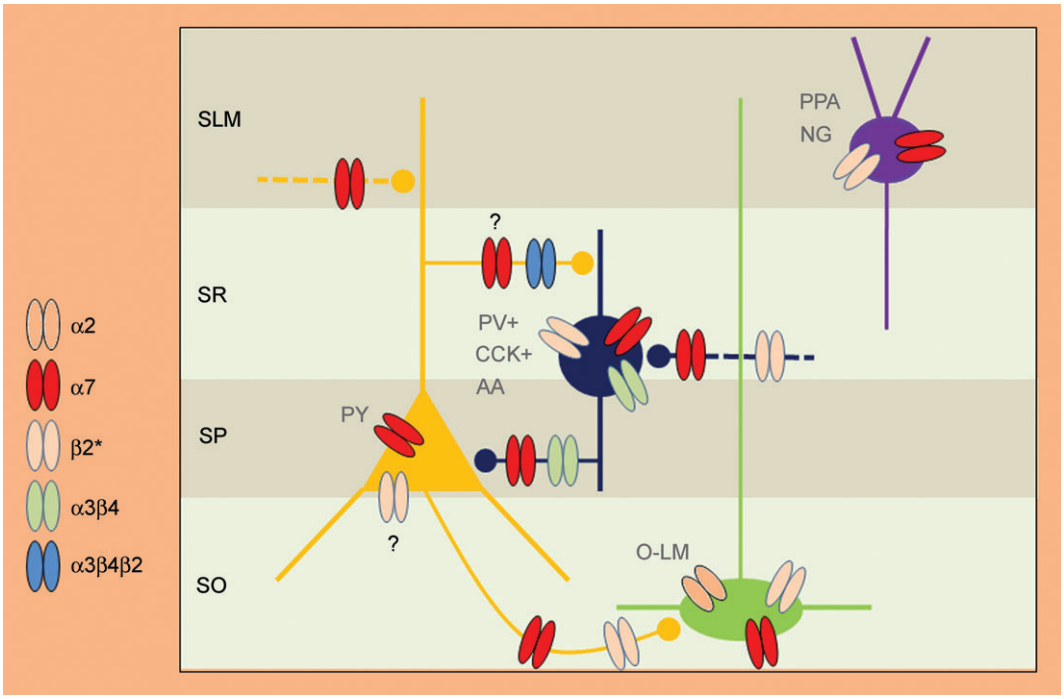

Figure 2. Simplified view of the expression of different nAChR subtypes on pyramidal cells and GABAergic interneurons present in the CA1 hippocampal region
SLM, stratum lacunosum moleculare; SR, stratum radiatum; SP, stratum pyramidale; SO, stratum oriens; PY, pyramidal cells; PV+, parvalbumin-positive; CCK+, cholecystokinin-positive; AA, axo-axonic interneurons; O-LM, oriens-lacunosum moleculare; PPA, perforant path-associated lacunosum moleculare or lacunosum moleculare-radiatum interneurons; NG, neurogliaform cell. Dashed lines represent glutamatergic terminals from pyramidal cells (yellow) or from GABAergic interneurons (blue).

densities of expression of voltage-gated sodium and potassium channels (Atzori *et al.* 2000; Martina *et al.* 2000; Lien *et al.* 2002; Lien & Jonas, 2003; Lawrence *et al.* 2006*a*). Moreover, they are endowed with hyperpolarization-activated channels (HCNs) carrying I_h, which underlies their pacemaker properties (Maccaferri & McBain, 1996; Ali & Thomson, 1998; Minneci *et al.* 2007) and with calcium-dependent potassium channels (BK and SK), which control action potential repolarization and the afterhyperpolarization (AHP), respectively (Zhang & McBain, 1995*a*,*b*). *In vivo* studies have demonstrated that during theta oscillations, O-LM cells become very active and, in cooperation with bistratified cells, modulate the dendrites of pyramidal cells one-quarter of a theta cycle after parvalbumin-expressing basket cells discharge (Klausberger & Somogyi, 2008). The O-LM firing is suppressed during ripple episodes (Klausberger *et al.* 2003). Furthermore, *in vitro* studies have shown that O-LM interneurons exhibit intrinsic resonance and spike transfer frequency preference within the theta range (Gillies *et al.* 2002; Pike *et al.* 2000; Hájos *et al.* 2004; Gloveli *et al.* 2005).

We used transgenic mice expressing enhanced green fluorescent protein in a subpopulation of stratum oriens interneurons containing somatostatin (Oliva *et al.* 2000) to assess the functional role of nAChRs on the firing properties of O-LM cells. Hence, we found that the post-synaptic calcium increase through calcium-permeable nAChRs and voltage-dependent calcium channels, activated by the depolarizing action of nicotine, facilitates the mobilization of calcium from intracellular stores.

This, in turn, activates apamin-sensitive calcium-dependent potassium conductances responsible for cell firing adaptation (Griguoli *et al.* 2009; Fig. 3). This effect follows the initial one consisting in an enhanced cell firing caused by the opening of cation-permeable channels (see also McQuiston & Madison, 1999) and probably mediated by non-desensitizing α2-containing nAChRs (Jia *et al.* 2009). Calcium increase via calcium-induced calcium release mechanisms will contribute to the prolongation of the effects of nicotine on firing adaptation. Like O-LM interneurons, auditory outer hair cells in the cochlea present a unique inhibitory synapse that uses a calcium-permeable excitatory acetylcholine receptor to activate hyperpolarizing currents mediated by SK channels (Art *et al.* 1984; Fuchs & Murrow, 1992; Blanchet *et al.* 1996). Previous studies from stratum oriens interneurons have demonstrated that cholinergic signalling via muscarinic receptors is crucial for tuning active conductances and for enhancing cell firing reliability (Lawrence *et al.* 2006*a*,*b*). Therefore, the dynamic integration of muscarinic and nicotinic signals will differentially control the firing properties of O-LM interneurons and rhythmogenesis.

nAChRs control activity-dependent synaptic plasticity processes

It is well known that nicotine, the neuroactive component of tobacco, enhances certain forms of memory (Rezvani & Levin, 2001). This occurs through nAChRs, highly expressed at pre- and post-synaptic sites in brain areas controlling learning and memory processes. In the hippocampus, a brain structure essential for encoding new declarative memories, nicotine has been shown to facilitate long-term potentiation (LTP) and convert short-term potentiation (STP) to LTP (Fujii *et al.* 1999; McGehee, 2002; Mann & Greenfield, 2003; Nashmi *et al.* 2007). The direction of synaptic changes (LTP or long-term depression, LTD) is strictly dependent on the localization of nAChRs and on the timing of their activation (Ji *et al.* 2001; Ge & Dani, 2005). For example, activation of nAChRs on CA1 pyramidal neurons can boost STP to LTP while stimulation of nAChRs on nearby interneurons can block LTP (Ji *et al.* 2001). In addition, exogenously applied ACh may convert STP to LTP or LTD, depending on the timing relative to afferent stimulation (Ge & Dani, 2005). In a series of elegant experiments, Gu & Yakel (2011), using electrophysiological and optogenetic tools, have demonstrated that different types of synaptic plasticity could be elicited in CA1 principal cells depending on the timing of the septal cholinergic input related to the Schaffer collateral input. Thus, stimulation of cholinergic afferents 100 ms or 10 ms prior to the Schaffer collateral resulted in α7 nAChR-dependent LTP or short-term depression (STD), respectively. It would be of interest to know how the precise timing of cholinergic modulation of synaptic plasticity at glutamatergic synapses affects local inhibitory circuits and rhythmogenesis.

In stratum radiatum interneurons, activation of α7 nAChRs by local photolysis of caged carbachol has been shown to significantly enhance cytoplasmic calcium levels in the perisomatic area (Khiroug *et al.* 2003). However, in these experiments, the extension of nAChR-mediated responses was probably underestimated due to dendritic filtering. More recently, calcium transients induced by activation of extrasynaptic nAChRs could be revealed also on dendrites of stratum radiatum interneurons (Rózsa *et al.* 2008). Dendritic calcium signalling, which increases as a function of the distance from the soma, interacts with back-propagating action potentials and, depending on the timing of α7 nAChR activation, may either potentiate or depress excitatory postsynaptic potentials. This cholinergic switch may be relevant for memory encoding and retrieval (Chang & Gold, 2003).

It is worth mentioning that a novel form of short-term plasticity involving extrasynaptic nAChRs, which closely depends on the time of agonist exposure and on the interval between exposures, has been described in stratum radiatum interneurons. By combining a dual-pulse

uncaging protocol with patch clamp recordings, Klein & Yakel (2005) have found that at short intervals (less than 200 ms) the second α7 nAChR-mediated response evoked by photolysis of caged carbachol is potentiated whereas at longer intervals it is depressed, probably because of nAChR desensitization. The potentiating effect is mediated by calcium-dependent processes and requires receptor phosphorylation. Calcium-permeable nAChRs may also modulate the activity of other nearby localized receptors. Two recent studies (Wanaverbecq *et al.* 2007; Zhang & Berg, 2007) have demonstrated that calcium increase via α7 nAChRs, activated by direct application of nicotine or by endogenously released ACh, down-regulates $GABA_A$-mediated synaptic currents. This effect can be favoured by the co-clustering of α7 nAChRs with $GABA_A$ receptors (Zago *et al.* 2006) but may occur also at distant sites via volume transmission (Umbriaco *et al.* 1995). The depressant effect which involved the activation of PKC, calcium–calmodulin-dependent protein kinase II and mitogen-activated protein kinase (MAPK), was clearly postsynaptic since it was blocked by chelating calcium in the postsynaptic cell and was not associated with modification in the paired-pulse ratio, a clear index of presynaptic release probability (Zucker, 1989). Whether the observed effect can be attributed to PKC-driven $GABA_A$ receptor phosphorylation or receptor internalization remains to be clarified. Interestingly, in the presence of α7 nAChR antagonists no run-down of whole cell GABAergic currents occurred, suggesting that in physiological conditions, $GABA_A$ receptors are controlled by ACh endogenously released from cholinergic fibres (Zhang & Berg, 2007). Down-regulation of GABAergic

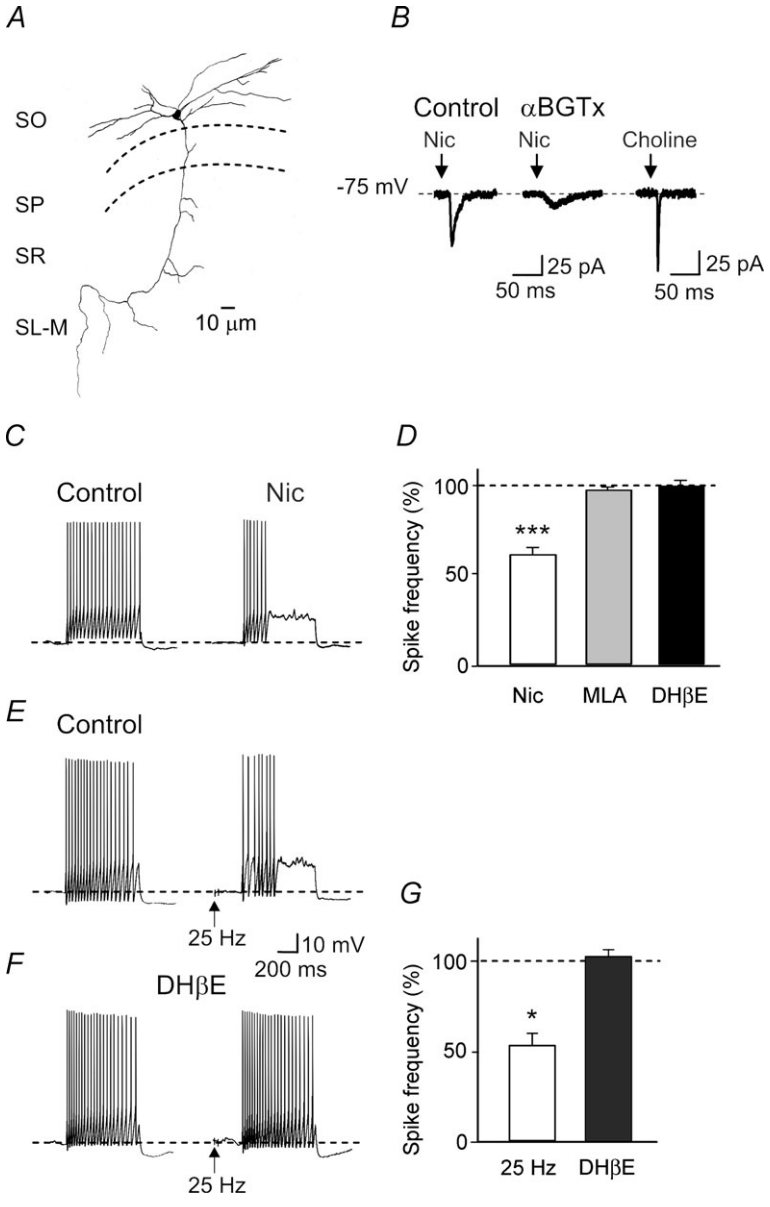

Figure 3. Activation of nAChRs by nicotine or endogenously released ACh reduces the firing rate of O-LM interneurons
A, camera lucida reconstruction of a O-LM cell. *B*, puff application of nicotine induces a fast inward current followed by a slow one. In the presence of αBGTx (100 nM, middle) a slow component is unveiled. Pressure application of choline to another cell induces a fast response. *C*, regular spiking interneuron in control and after bath application of nicotine. *D*, each column represents the mean spike frequency values (expressed as percentage of control, dashed line), obtained in the presence of nicotine ($n = 21$) and nicotine plus MLA ($n = 16$) or DHβE ($n = 16$). *E*, a regular spiking neuron recorded before (Control) and immediately after delivering one train of high-frequency stimuli (2 s duration at 25 Hz) to cholinergic fibres in the alveus (in the presence of atropine). *F*, as in *E* but in the presence of a high (50 μM) concentration of DHβE. *G*, each column represents the mean spike frequency values obtained after stimulation of cholinergic fibres in the absence (open, $n = 8$) or in the presence (filled, $n = 8$) of DHβE and expressed as percentage of control (dashed line). $^*P < 0.05$; $^{***}P < 0.001$. Modified from Griguoli *et al.* 2009.

signalling may potentiate NMDA-mediated synaptic currents in principal cells and facilitate LTP induction, as demonstrated at CA3–CA1 synapses (Yamazaki *et al.* 2005, 2006),

At excitatory synapses between CA1 pyramidal cells and O-LM interneurons, a novel NMDA-independent form of LTP has been recently described (Lamsa *et al.* 2007). This form of LTP requires the activation of calcium-permeable AMPA receptors and type I mGluRs, and it has been named anti-Hebbian because presynaptic activation coincides with postsynaptic quiescence. This occurs when high-frequency stimulation (HFS) of presynaptic fibres is delivered to postsynaptic neurons maintained hyperpolarized (Lamsa *et al.* 2007; Le Duigou & Kullmann, 2011). Calcium-permeable AMPA receptors exhibit, in fact, a strong inward rectification that favours calcium entry at hyperpolarizing membrane potentials. Calcium rise via calcium-permeable AMPA receptors and mGluRs would activate a transduction pathway necessary for LTP induction. It would be of interest to test whether cholinergic signalling via nAChRs and mAChRs (activated by ACh released from cholinergic fibres during HFS) may contribute to anti-Hebbian LTP. It is known that, as calcium-permeable AMPA receptors, nAChRs exhibit a pronounced inward rectification (Bertarnd *et al.* 1993) due to polyamine block at depolarizing potentials (Haghighi & Cooper, 1998), a condition that favours calcium entry at relatively negative membrane potentials. In addition, since the concentration of polyamines in the cytoplasm could be dynamically regulated and nAChRs are several times more sensitive to spermine block than AMPA receptors (Haghighi & Cooper, 1998), it may be possible that their attenuation following repetitive synaptic activation (Rozov & Burnashev, 1999) will preferentially block nAChRs, promoting in this manner calcium flux via these receptor types.

Conclusions

The data reviewed here clearly indicate that cholinergic signalling via nAChRs plays a crucial role in regulating local GABAergic circuits in the hippocampus. Much remains to be discovered about the underlying cellular and molecular processes. In particular, most of the reported studies failed to characterize how nAChR signalling regulates the activity of well-identified interneuronal subtypes. In addition, it is unclear how nAChR-mediated changes in synaptic efficacy may affect the dynamic properties of the hippocampal circuit, rhythmogenesis, and how these functional changes relate to behaviour. These have important implications not only for the understanding of how information is stored and processed in the brain but also for pathological conditions including Alzheimer's and Parkinson's diseases and schizophrenia in which a cholinergic dysfunction parallels the loss of high cognitive functions (Kenney & Gould, 2008).

Selectively activating or silencing cholinergic input in specific neuronal ensembles using optogenetic tools will allow the correlation of hippocampal microcircuit functional structure with animal behaviour in both physiological and pathological conditions.

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