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SYMPOSIUM REVIEW

Neurogliaform cells and other interneurons of stratum lacunosum-moleculare gate entorhinal–hippocampal dialogue

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The stratum lacunosum-moleculare of the hippocampus is an area of integration that receives inputs from extrinsic excitatory fibres including those from the entorhinal cortex, and is under the control of several neuromodulators. A critical aspect is the presence in this hippocampal layer of specific interneurons that are likely to influence the strength and the temporal structure of entorhinal–CA1 hippocampal dynamics. I review here recent data on the physiological role of these interneurons. Special focus is devoted to one interneuron type, the so-called neurogliaform cell, because recent studies have defined its unusual mode of cell-to-cell communication. Neurogliaform cells mediate feedforward inhibition of CA1 pyramidal cells, form a network of cells connected via chemical and electrical synapses, and evoke slow inhibitory synaptic currents mediated by $GABA_A$ and $GABA_B$ receptors. The modulation of entorhinal input by neurogliaform cells and their contribution to network theta rhythm are also discussed. I hope that novel information on neurogliaform cells will contribute to the ever-growing appreciation of GABAergic cell type diversity, and will inspire neuroscientists interested not only in synaptic physiology but also in the brain's spatial representation system.

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Diversity in GABAergic cells of the stratum lacunosum-moleculare

The so-called stratum lacunosum-moleculare (SLM) is a hippocampal layer close to the hippocampal fissure and the dentate gyrus. This layer of the hippocampus is important because it serves as a relay between the entorhinal cortex (EC) and the CA1 hippocampus. The synaptic dialogue occurring between these two brain areas is crucial for several brain operations in health and in neurological diseases. For example, entorhinal–hippocampal interactions are believed to represent the substrate of distinct aspects of spatial and episodic memory (Moser *et al.* 2008). Furthermore, neurons of the human entorhinal cortex that send projections to the CA1 hippocampus are the first degenerating cells in Alzheimer's disease (Braak & Braak, 1993). The SLM is an area of integration because it contains not only the terminals of fibres originating from layer III of the EC (Witter *et al.* 1988), but also from other brain areas, such as the nucleus reuniens of the midline thalamus (Wouterlood *et al.* 1990), the amygdaloid

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complex (Pikkarainen *et al.* 1999), and the inferotemporal cortex (Iwai & Yukie, 1988).

The entorhinal afferents (the temporoammonic or perforant path) contact not only the apical tuft of CA1 pyramidal cells but also interneurons of the SLM (Desmond *et al.* 1994), which they powerfully excite (Lacaille & Schwartzkroin, 1988*a*). A variety of interneurons are present in the SLM. But what makes a cell an interneuron of the SLM? Is it the presence in this layer of its soma, dendrites, axon, or of all of these components? We define here an interneuron of the SLM as a GABAergic cell with at least the soma in this layer. Interneurons with some of their dendrites in the SLM but with the soma in other layers, such as axo-axonic cells (Somogyi *et al.* 1985; but see Ganter *et al.* 2004), are also known. Such cells should also be activated by the temporoammonic path and other excitatory fibres of the SLM, perhaps sharing with interneurons of the SLM common functions.

How is cell diversity gauged? Currently, GABAergic interneurons are classified mainly based on their innervations of selected sub-cellular domains of post-synaptic cells, their molecular expression profiles and their firing patterns. The aim of this article is to review the physiological role of GABAergic cells of the SLM with special attention to the so-called neurogliaform cells. A classic review summarises earlier knowledge on GABAergic neurons of the hippocampus, including the SLM (Freund & Buzsaki, 1996). More recently, several GABAergic cell types with the soma in the SLM or at the stratum radiatum (SR)–SLM border have been recognised (Fig. 1) (Acsády *et al.* 1996; Hajos & Mody, 1997; Cossart *et al.* 1998; Vida *et al.* 1998; Cope *et al.* 2002; Pawelzik *et al.* 2002; Klausberger *et al.* 2005; Price *et al.* 2005; Ali, 2007; Elfant *et al.* 2008; Klausberger & Somogyi, 2008; Klausberger, 2009; Fuentealba *et al.* 2010; Ali & Todorova, 2010). One of these is the basket cell whose axon branches mainly in the pyramidal cell layer; most, but not all of them, are positive for cholecystokinin (CCK) and/or vasoactive intestinal polypeptide (VIP). Another type is the Schaffer collateral/commissural pathway-associated interneuron, the axon of which ramifies in the SR, and sometime also in stratum oriens, targeting the oblique and basal dendrites of pyramidal cells. Some of these latter neurons express CCK, but also calbindin. A further cell type is the so-called apical dendrite innervating cell. This interneuron is similar to the Schaffer collateral/commissural pathway-associated cell, but it targets preferentially the main apical shaft of CA1 pyramidal cells and can express CCK, cannabinoid (CB) receptor 1, vesicular glutamate transporter (VGLUT) 3 and the neurokinin 1 receptor. The perforant path-associated interneuron innervates the apical tuft of CA1 pyramidal cells and the dendrites of granule cells of the dentate gyrus, namely the perforant path termination zone. It

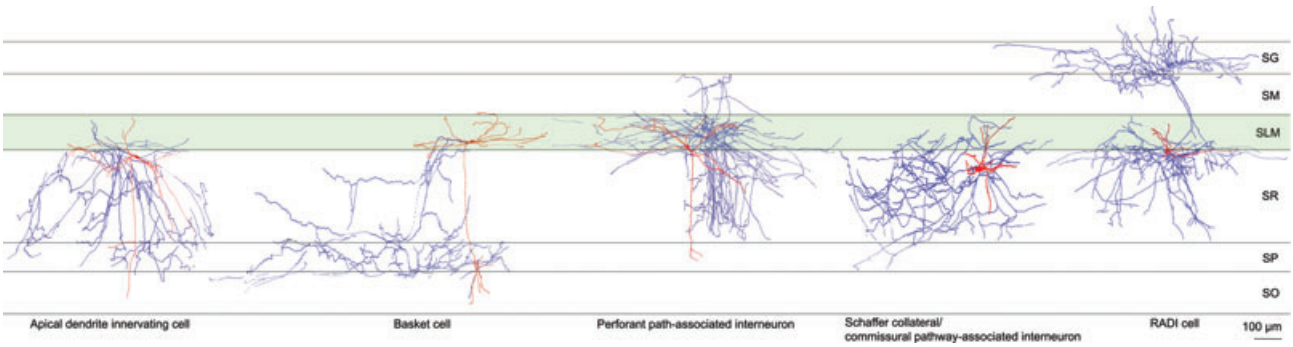

Figure 1. Diversity of interneurons with the soma in the SLM or at the SR–SLM border
The location of the soma and the axodendritic distribution of selected hippocampal interneurons are illustrated in this composite drawing; soma and dendrites are shown in red, the axonal arborization is shown in blue. Apical dendrite innervating cell, basket cell, perforant path-associated interneuron, and RADI cell are partial reconstructions from *in vivo* extracellularly recorded cells of rat individually labelled with neurobiotin using the juxtacellular labelling method (images adapted with permission from Klausberger *et al.* (2005), and Fuentealba *et al.* (2010)). The Schaffer collateral/commissural pathway-associated interneuron has been visualised after immunocytochemistry of a rat hippocampal acute slice *in vitro* containing the recorded neuron filled with biocytin (image adapted with permission from Cope *et al.* (2002)). Note that the soma of this cell is located in the stratum radiatum. Schaffer collateral/commissural pathway-associated interneurons with the soma at the SR–SLM border have also been shown in other papers (e.g. Vida *et al.* 1998 and Pawelzik *et al.* 2002). In each of the latter cases the axonal pattern is less clear than shown here, because the axon was intermingled with the axon of another reconstructed cell. Note the different axonal patterns of the various cell types illustrated. To allow the reconstructions to be shown with linear layer boundaries and with the same layer thicknesses for all cells, while maintaining the locations of all processes relative to the layer boundaries, 'liquify filters' were applied in Adobe Photoshop. Therefore, the borders of the hippocampal layers marked by thin lines do not inform about the thickness of each layer. Abbreviations: RADI, radiatum- and dentate-innervating; SO, stratum oriens; SP, stratum pyramidale; SR, stratum radiatum; SLM, stratum lacunosum-moleculare; SM, stratum moleculare; SG, stratum granulosum.

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can be immunopositive for CCK, calbindin or the CB1 receptor. Recently, a potential novel interneuron type with the soma at the SLM–SR border has been reported, and termed the radiatum- and dentate-innervating (RADI) cell (Fuentealba *et al.* 2010). The most striking feature of this cell is its pronounced innervation of granule cells. The RADI cell is immunopositive for the transcription factor COUP-TFII, calbindin, the neuropeptide precursor pre-protachynin B (PPTB) and CB1 (Fuentealba *et al.* 2010). *In vivo*, the above mentioned GABAergic cells exhibit differential spike timing during network oscillations (Klausberger, 2009). In addition to these 'local' interneurons, a GABAergic 'long-range projecting' cell type with the soma at the SLM–SR border has been reported and called the radiatum retrohippocampal projection neuron (Jinno *et al.* 2007). This cell sends projections to a variety of extra-hippocampal areas including the subiculum, presubiculum, retrosplenial cortex and indusium griseum.

The heterogeneity of SLM interneurons is indicative of their functional diversity. However, information on the synaptic inhibition generated by each of these cell types is scant (Vida *et al.* 1998). One exception is represented by the neurogliaform cell (NGFC). This interneuron type is frequently encountered in the SLM and displays a unique mode of communication with its target cells (Price *et al.* 2005; Price *et al.* 2008; Karayannis *et al.* 2010), consistent with observations on NGFCs in the neocortex (Tamas *et al.* 2003; Simon *et al.* 2005; Olah *et al.* 2007; Szabadics *et al.* 2007; Olah *et al.* 2009), and in the dentate gyrus of the hippocampus (Armstrong *et al.* 2011). Therefore, the remainder of this article will focus on NGFCs of the hippocampal SLM.

Neurogliaform cells mediate slow synaptic inhibition

The NGFC is probably the most compact interneuron of the SLM since it has a small soma and dendrites arranged in a stellate fashion around it, resembling a glial cell, hence its name (Figs 2 and 3). The hallmark of the NGFC is its axon, which branches profusely and produces an unusually dense arbour localised within the SLM, the SR–SLM border and/or the molecular layer of the dentate gyrus (Khazipov *et al.* 1995; Vida *et al.* 1998; Price *et al.* 2005, 2008; Fuentealba *et al.* 2010; Karayannis *et al.* 2010). Recently, NGFCs have been identified using a combination of different marker proteins. These include: α-actinin2, neuropeptide Y, neuronal nitric oxide synthase (nNOS), the transcription factor COUP-TFII, the extracellular matrix protein reelin, and the $GABA_A$ receptor α_1 and δ subunits (Price *et al.* 2005; Olah *et al.* 2009; Fuentealba *et al.* 2010). NGFCs are of heterogeneous embryonic origin, namely nNOS-positive NGFCs deriving from the medial ganglionic eminence, whereas nNOS-negative NGFCs originate from the caudal ganglionic eminence (Tricoire *et al.* 2010). Thus, distinct subpopulations of NGFCs are likely to exist. *In vitro*, hippocampal NGFCs of rodents display characteristic late firing when stimulated with a depolarizing current pulse just above threshold (Price *et al.* 2005). *In vivo*, the firing of NGFCs is modulated by hippocampal rhythms (Fuentealba *et al.* 2010). During theta oscillations, the probability of NGFC firing is maximal just after the peak of the cycle recorded extracellularly in the stratum pyramidale, coincident with the synaptic volley from the EC. Furthermore, the probability of NGFC firing is enhanced during the trough of gamma oscillations recorded in the SLM and decreased or not changed during faster ripple oscillations (Fuentealba *et al.* 2010).

A NGFC receives monosynaptic, fast excitatory inputs from the temporoammonic path (Fig. 3) and from the Schaffer collaterals, the axons of CA3 pyramidal cells; the resultant EPSC displays both AMPA and NMDA receptor components (Price *et al.* 2005). These EPSCs facilitate and then depress or only depress upon repetitive stimulation at theta frequency (Price *et al.* 2005), but long-term synaptic plasticity has not been reported so far. NGFCs are not activated by the stimulation of CA1 pyramidal cells (Price *et al.* 2005), and therefore they represent a rare case of a 'pure' feedforward interneuron (Alger & Nicoll, 1982). Spontaneous IPSCs with heterogeneous kinetics are also detected in NGFCs (Karayannis *et al.* 2010). Interestingly, NGFCs have often been found to synaptically couple with each other and this has led to the conclusion that they form a specific interneuronal network (Price *et al.* 2005). In addition and consistent with this proposal, electrical coupling between NGFCs, and also with other types of interneurons, occurs acting as a low pass filter (Price *et al.* 2005; Zsiros & Maccaferri, 2005). Interneurons with the soma in the stratum oriens and with the axon branching in the SLM, such as the so-called oriens–lacunosum-moleculare (O-LM) interneuron (McBain *et al.* 1994), also make synapses with NGFCs (Elfant *et al.* 2008). A unitary IPSC with fast kinetics has been detected in a NGFC after the stimulation of a single O-LM cell (Elfant *et al.* 2008). The O-LM cell receives robust excitatory inputs from CA1 pyramidal cells (Lacaille *et al.* 1987), and therefore it acts as a feedback interneuron (Maccaferri & McBain, 1995). We have proposed that the activation of oriens–SLM inhibitory synapses shifts the balance from feedforward to feedback inhibition of CA1 pyamidal cells (Elfant *et al.* 2008).

Typically, the output of NGFCs consists of slow postsynaptic inhibitory currents (IPSCs) (decay time constant >30 ms) onto all their target cells identified so far (Fig. 2). These include other NGFCs, other types of interneurons, pyramidal cells, and even themselves, through autaptic connections (Price *et al.* 2005, 2008; Karayannis *et al.* 2010). Interestingly, NGFC-IPSCs resemble $GABA_{A,slow}$ IPSCs reported earlier in CA1 pyramidal cells after the

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extracellular stimulation of the SLM or the SR–SLM border (Pearce, 1993). All the evidence accumulated so far is consistent with the idea that the NGFC represents a major source of $GABA_{A,slow}$ in the hippocampus. Unitary IPSCs with slow kinetics (although faster than those evoked by NGFCs) have also been recorded in CA1 pyramidal cells after the stimulation of another abundant hippocampal GABAergic cell type, the so-called Ivy cell (Fuentealba *et al.* 2008). In addition to such slow $GABA_A$ receptor-mediated IPSC, and unique amongst GABAergic cells, a single action potential in a NGFC also elicits a small slow unitary IPSC mediated by $GABA_B$ receptors (Price *et al.* 2005, 2008). This is consistent with earlier results showing that slow inhibitory events are evoked in CA1 pyramidal cells after the stimulation of non-identified interneurons of the SLM (Lacaille & Schwartzkroin, 1988*b*). Upon repetitive stimulation, NGFC-IPSCs depress strongly, and this short-term plasticity is under the tight control of presynaptic $GABA_B$ receptors (Price *et al.* 2005, 2008). When the NGFC firing occurring *in vivo* is replayed in NGFCs *in vitro* it evokes an even stronger and longer lasting synaptic depression (recovery time constant ∼10 min), independent from $GABA_B$ receptors (Karayannis *et al.* 2010). This robust synaptic depression is specific to NGFC-IPSCs because it does not occur with unitary IPSCs evoked by other types of interneurons of the SLM (Karayannis *et al.* 2010). It is currently not known whether a similar synaptic depression also occurs *in vivo* when NGFCs fire several action potentials in short succession (Fuentealba *et al.* 2010).

What are the mechanisms underlying the slow $GABA_A$ receptor mediated NGFC-IPSC? One important factor is the unique spatiotemporal profile of extracellular GABA released by these interneurons. In this respect, it is remarkable that a single NGFC axon can contain a

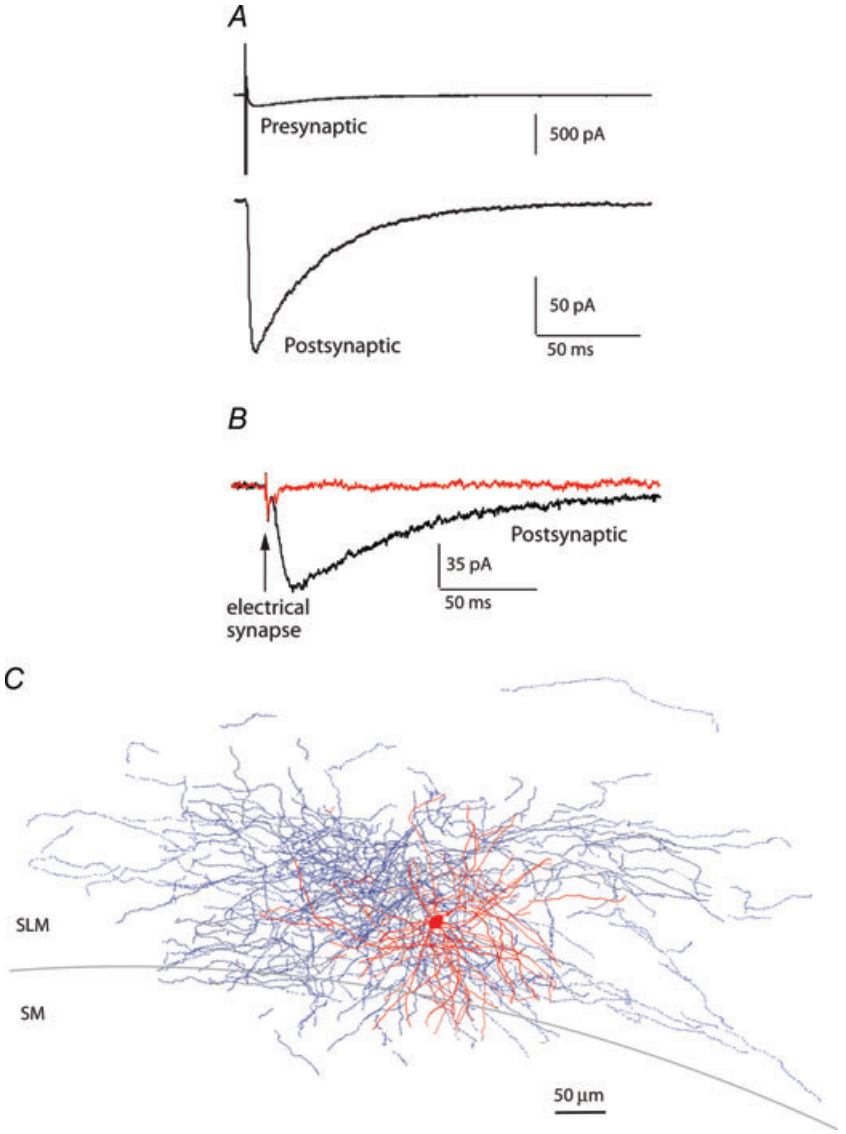

Figure 2. Activation of NGFC of the SLM evokes slow IPSCs
A, a short square depolarizing voltage pulse applied to a presynaptic NGFC elicits a fast initial action current (top trace), which in turn evokes a slow IPSC (decay time constant > 30 ms) in a postsynaptic NGFC (bottom trace). *B*, unitary NGFC-IPSCs in control conditions (black, in the presence of 5 μM CGP55845, a $GABA_B$ receptor antagonist) and abolished by the $GABA_A$ receptor antagonist SR95531 (5 μM, red). Note that the presynaptic trace is omitted, and the fast transient inward current (arrow) indicating an electrical connection. *C*, light microscopic reconstruction (×100) of a biocytin-labelled NGFC (soma and dendrites in red, axon in blue) in rat acute slice. The axonal arbour remains largely restricted to the stratum lacunosum-moleculare (SLM) but at some locations crosses the hippocampal fissure into the stratum moleculare. Note also that the axon overlaps extensively with the dendritic arbour forming putative autaptic contacts. Abbreviations: SLM, stratum lacunosum-moleculare; SM, stratum moleculare. Adapted, with permission, from Karayannis *et al.* (2010).

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density of release sites which is comparable to that of five to six basket cell axons (Olah *et al.* 2009). This structural arrangement has been recently shown to mediate volume transmission whereby GABA released from NGFC axons reaches synaptic and non-synaptic sites on target neurons (Olah *et al.* 2009). Synapses formed by NGFCs are often (but not always) up to 1–5 μm away from target dendrites (Tamas *et al.* 2003; Price *et al.* 2005; Szabadics *et al.* 2007; Olah *et al.* 2009; Fuentealba *et al.* 2010; Karayannis *et al.* 2010). Functional tests demonstrate that GABA released from NGFCs inhibits the release of glutamate or GABA from axon terminals which are located at some distance from NGFC release sites (Olah *et al.* 2009). Volume transmission is likely to generate a prolonged, low-level GABA transient at NGFC synapses bringing about the slow kinetics of NGFC-IPSCs. Indeed, the duration of the GABA transient at NGFC synapses appears to be exceptionally long, as suggested by recent experimental and computational data (Karayannis *et al.* 2010) including tests with competitive antagonists with different affinities for the $GABA_A$ receptor. The latter approach probes changes in the amplitude and waveform of unitary IPSCs caused by application of competitive antagonists at sub-saturating concentrations (Overstreet *et al.* 2002). If GABA dwells in a particular synaptic cleft longer than the unbinding time of the antagonist, the result could be a prolonged IPSC rising phase. The competitive antagonist 1,2,5,6-tetrahydropyridin-4-yl-methylphosphinic acid (TPMPA), with low affinity and fast unbinding rate ($\sim$0.6 ms) (Jones *et al.* 2001), significantly increases the rise time of NGFC-IPSCs but not fast IPSCs (Karayannis *et al.* 2010). This result suggests that GABA released by NGFCs stays in the cleft longer than GABA released by other interneurons mediating fast IPSCs. Such antagonist-induced IPSC prolongation is also observed in simulations, in which NGFC-IPSCs are best fitted by a low-concentration GABA transient (range: 8–20 μM) that persists for an unusually long time (decay time constant range: 35–73 ms) (Karayannis *et al.* 2010). Consistent with this view are also the observations that (i) a single presynaptic action potential in a NGFC elicits a $GABA_B$ receptor-mediated IPSC, as mentioned above, (ii) GABA uptake blockers enhance both the $GABA_A$ receptor mediated and the $GABA_B$ receptor mediated components of NGFC-IPSCs, especially as the latter is mediated by extrasynaptic receptors, and (iii) a low-affinity $GABA_A$ receptor antagonist has a greater inhibitory effect on NGFC-IPSCs *versus* fast IPSCs (Szabadics *et al.* 2007; Karayannis *et al.* 2010).

In principle, an additional mechanism that could be responsible for the slow kinetics of the NGFC-IPSCs is the subunit composition of $GABA_A$ receptors; this factor is believed to determine the kinetics of IPSCs at several CNS synapses (Farrant & Kaila, 2007). Experimentally, slow IPSCs impinging on CA1 pyramidal cells, but not on interneurons, are impaired in the hippocampus of $GABA_A$ β_3 subunit null mice (Hentschke *et al.* 2009). Moreover, the $GABA_A$ α_5 subunit appears to be involved in NGFC-IPSCs (Karayannis *et al.* 2010) and in slow IPSCs recorded from pyramidal cells (Zarnowska *et al.* 2009). Finally, $GABA_A$ α_1 subunit agonists strongly modulate NGFC-IPSCs (Szabadics *et al.* 2007; Karayannis *et al.* 2010), and this subunit is enriched in hippocampal NGFC dendrites (Fuentealba *et al.* 2010) that receive a substantial input from other NGFCs (Price *et al.* 2005). Overall, most of the evidence available indicates that $GABA_A$ receptor kinetics may contribute to, but do not necessarily account for, NGFC-IPSCs. In addition to the neurotransmitter profile and the receptor subunit composition, unusual kinetic properties of the synaptic release machinery in NGFC terminals could also contribute to shape slow IPSCs. Interestingly, synaptic vesicles have been detected far away from synaptic specialisations in the axonal plexus of NGFCs (Olah *et al.* 2009) and also of hippocampal Ivy cells (Fuentealba *et al.* 2008), indicating the possibility of extrasynaptic transmitter release. This structural arrangement might be related to the recent

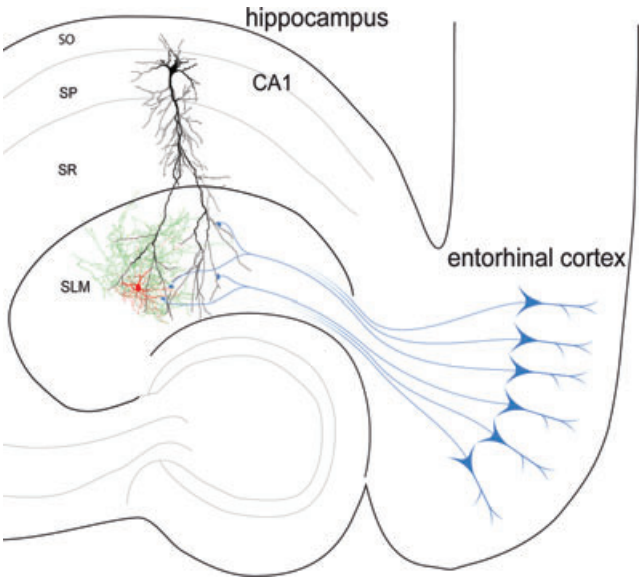

Figure 3. Information between the entorhinal cortex and the CA1 hippocampus is gated by NGFCs in the SLM
Simplified scheme of rodent entorhinal cortex-CA1 hippocampus highlighting the location of a NGFC in the SLM. Several other interneuron types have been detected with the soma in the SLM, but they are not illustrated here. Reconstruction of a NGFC (soma and dendrites, red lines; axon, green lines) synaptically coupled to a CA1 pyramidal cell (soma and partial reconstruction of dendrites, black lines) is illustrated; modified, with permission, from Price *et al.* (2008). Shown schematically are also pyramidal cells of layer III of the entorhinal cortex that send projections and make synaptic contacts onto the apical tuft of the CA1 pyramidal cell and onto the NGFC. See text for more details. Abbreviations: SO, stratum oriens; SP, stratum pyramidale; SR, stratum radiatum; SLM, stratum lacunosum moleculare.

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finding that the duration of calcium transients at NGFC axonal boutons is about three times longer than at the boutons of other types of hippocampal interneurons (Karayannis *et al.* 2010).

Role of interneurons of SLM in gating entorhinal–hippocampal interactions

It has been reported that the stimulation of the EC evokes EPSPs and action potentials in CA1 pyramidal cells *in vivo* and EPSPs *in vitro* (Soltesz & Jones, 1995). However, strong IPSPs are also detected after electrical stimulation of the EC *in vivo*, especially with low-frequency stimulation (<0.1 Hz) (Soltesz & Deschenes, 1993), and after temporoammonic path stimulation *in vitro* (Empson & Heinemann, 1995*a*). More recently, it was found that temporoammonic path activation generates dendritic spikes that are facilitated in their propagation to the soma by the temporally locked activity of Schaffer-collateral inputs (Jarsky *et al.* 2005). Feedforward inhibition generated by interneurons of the SLM temporally limits the excitatory influence of the temporoammonic path (Price *et al.* 2008) and narrows the time window for facilitation of dendritic spike propagation by Schaffer collateral EPSPs (Jarsky *et al.* 2005).

It has been proposed that networks of interneurons are critical in determining the temporal structure of spatially organized neuronal ensembles (Buzsaki & Chrobak, 1995). Therefore the roles of interneurons of the SLM should be mostly prominent when network activities, and notably oscillatory rhythms, are considered. In this respect, theta and gamma rhythms generated in the entorhinal cortex can drive similar activity in the hippocampus. Theta (4–8 Hz) oscillations are observed during REM sleep, arousal, locomotion, and other voluntary behaviours; they are believed to mediate memory formation and recall (Buzsaki, 2002). Interestingly, theta oscillations are most regular in frequency, and have the largest amplitude, in the SLM of the CA1 hippocampus (Bragin *et al.* 1995). Recently, the firing of EC and hippocampal neurons has been recorded during theta rhythm in non-anaesthetized rats *in vivo* and their temporal relationships examined (Mizuseki *et al.* 2009). The temporal delays between population activities in the EC and in the CA1 hippocampus was found to be longer (by half a theta cycle) than expected solely from axonal conduction velocities and passive synaptic integration of feed-forward excitatory inputs. It is possible that this delay is due to local computations provided by interneurons of the SLM, in addition to other factors (Mizuseki *et al.* 2009).

Phasic entorhinal activity, which evokes feed-forward inhibition in pyramidal cells (Empson & Heinemann, 1995*b*), drives the activity of interneurons of the SLM (Remondes & Schuman, 2002), which in turn rhythmically silence the somatically projecting interneurons at theta frequency (Banks *et al.* 2000). This finding is consistent with intracellular recordings from pyramidal cells showing that dendritic theta is in antiphase with somatic theta (Kamondi *et al.* 1998). As mentioned above, NGFCs display an *in vivo* firing pattern that is time-locked to the peak of the theta cycle, coincident with the synaptic volley from the EC (Fuentealba *et al.* 2010). Remarkably, the duration of inhibitory events mediated by NGFCs, which is approximately 125 ms, is perfectly adapted to ensure a firing frequency of no more than ∼8 Hz. The NGFCs form an extensive network with other NGFCs, as well as with other interneurons in the SLM, through chemical and electrical contacts (Price *et al.* 2005; Zsiros & Maccaferri, 2005). The synchrony associated with electrical coupling between interneurons is a critical factor in generating oscillations in interneuronal networks (Hestrin & Galarreta, 2005), and the inhibitory influence of such networks can entrain pyramidal cells to their rhythm. Additionally, NGFCs and other interneurons of the SLM are inhibited by interneurons of the stratum oriens such as the O-LM cell, promoting a switch from feedforward inhibition to feedback inhibition of CA1 pyamidal cells (Elfant *et al.* 2008). The latter mechanism allows NGFCs to be silenced in favour of higher frequency pyramidal-cell oscillatory activity, and could contribute to the phase shift of theta oscillations observed from SLM to stratum oriens (Bragin *et al.* 1995). Another contributing factor is that intrinsic membrane potential theta oscillations are present in CA1 interneurons with the soma at the SR–SLM border (Chapman & Lacaille, 1999). Finally, it is important to consider that the axonal arborisations of NGFCs overlap spatially with excitatory terminals in the SLM (Fuentealba *et al.* 2010), suggesting NGFC-mediated inhibition of glutamate release from excitatory fibres terminating nearby. This mechanism has been recently shown to work via presynaptic $GABA_B$ receptors when activity of NGFC of the neocortex occurs (Olah *et al.* 2009). By using this 'presynaptic' mechanism, in addition to prolonged inhibition of postsynaptic cells, hippocampal NGFCs would promote inhibition of entorhinal–hippocampal interactions and down-scaling of activity in the SLM.

Conclusions and future directions

Significant progress has been made toward understanding the physiological role of interneurons of the SLM. Considerable evidence suggests that their prime physiological role consists of gating the dialogue between the entorhinal cortex and CA1 hippocampus. Recent research has identified the NGFC of the SLM as a hippocampal interneuron type that evokes $GABA_A$ and $GABA_B$ receptor mediated slow inhibition (Price *et al.* 2005, 2008). The mechanisms underlying slow $GABA_A$

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IPSCs appear to depend on the unique spatiotemporal profile of GABA present at NGFC synapses (Szabadics *et al.* 2007; Karayannis *et al.* 2010). This idea is consistent with the recent finding of volume transmission of GABA released by NGFCs (Olah *et al.* 2009). In this way NGFCs are likely to influence large numbers of neurons, glial cells and microvessels (Cauli *et al.* 2004). Furthermore, phase locked activity of NGFCs in relation to network rhythms has been reported (Fuentealba *et al.* 2010), showing that the maximal probability of their firing is coincident with the synaptic volley from the entorhinal cortex. There are excellent reasons to believe that future research on GABAergic cells of the SLM will bring exciting new discoveries. Future efforts should be directed at least in two directions. On the one hand, the unique features of NGFC synapses and the mechanisms underlying slow IPSCs should be further studied. In this respect, it will be important to clarify how conventional synapses (Tamas *et al.* 2003; Price *et al.* 2005; Olah *et al.* 2007; Fuentealba *et al.* 2010) and *en passant* boutons several micrometres away from target dendrites (Olah *et al.* 2009) can produce NGFC-IPSCs with similar slow kinetics. On the other hand, experiments designed to selectively suppress inhibition mediated by interneurons of the SLM *in vivo*, via genetic or selective pharmacological manipulations, will be particularly useful in improving our understanding of their physiological roles.

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