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REVIEW ARTICLE
GABAergic interneurons targeting dendrites of pyramidal cells in the CA1 area of the hippocampus

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Abstract

The dendrites of pyramidal cells are active compartments capable of independent computations, input/output transformation and synaptic plasticity. Pyramidal cells in the CA1 area of the hippocampus receive 92% of their GABAergic input onto dendrites. How does this GABAergic input participate in dendritic computations of pyramidal cells? One key to understanding their contribution to dendritic computation lies in the timing of GABAergic input in relation to excitatory transmission, back-propagating action potentials, Ca^{2+} spikes and subthreshold membrane dynamics. The issue is further complicated by the fact that dendritic GABAergic inputs originate from numerous distinct sources operating with different molecular machineries and innervating different subcellular domains of pyramidal cell dendrites. The GABAergic input from distinct sources is likely to contribute differentially to dendritic computations. In this review, I describe four groups of GABAergic interneuron according to their expression of parvalbumin, cholecystokinin, axonal arborization density and long-range projections. These four interneuron groups contain at least 12 distinct cell types, which innervate mainly or exclusively the dendrites of CA1 pyramidal cells. Furthermore, I summarize the different spike timing of distinct interneuron types during gamma, theta and ripple oscillations *in vivo*, and I discuss some of the open questions on how GABAergic input modulates dendritic operations in CA1 pyramidal cells.

Introduction

In the CA1 area of the hippocampus, similar to other cortical areas, pyramidal cells receive mainly glutamatergic and GABAergic synaptic inputs. Glutamatergic input from cortical pyramidal cells and subcortical sources transmits activity generated through sensory inputs as well as spontaneous activity of the nervous system. The GABAergic inputs, originating mainly from local interneurons, contribute to the formation of cell assemblies by regulating the activity of pyramidal cells. Local GABAergic interneurons control the firing rate of pyramidal cells and modulate their spike timing and synchronize their activity. In the hippocampus and isocortex, there is a large diversity of distinct types of GABAergic interneurons innervating different subcellular domains of pyramidal cells and operating with distinct molecular machineries (Ascoli *et al.*, 2008). Interneurons targeting the somata and proximal dendrites, called basket cells, and interneurons targeting specifically the axon initial segments, called axo-axonic cells, have been intensely investigated because of their potential to control the output of pyramidal cells. In addition, their concentrated synaptic release sites in the CA1 pyramidal cell layer onto somata and axon initial segments, which are also devoid of glutamatergic synapses, produce relatively large voltage changes in the extracellular space. Therefore, the activity of these interneurons makes major contributions to network oscillations in the hippocampal field. However, 92% of GABAergic synapses contacting CA1 pyramidal cells innervate their dendrites and not the somata and axon initial segments (Megias *et al.*, 2001). The dendrites of pyramidal cells contribute actively to input/output transformation, integration of information and synaptic plasticity (Hausser *et al.*, 2000; Chen & Johnston, 2006; Harvey & Svoboda, 2007; Spruston, 2008). Therefore, it is expected that dendritic GABAergic inputs regulate these dendritic computations of pyramidal cells.

In this review, first I describe four groups and 12 distinct types of GABAergic interneuron which innervate mainly the dendrites of CA1 pyramidal cells. I summarize the activity of the different interneuron types during network oscillations *in vivo*. Based on these spatio-temporal data, I discuss some open questions about GABAergic inputs to pyramidal cell dendrites.

GABAergic interneurons innervating mainly the dendrites of CA1 pyramidal cells

In the absence of phylogenetic information regarding hippocampal interneurons, I describe different GABAergic interneurons in the rat CA1 area of the hippocampus based on recent classification suggestions (Bota & Swanson, 2007; Ascoli *et al.*, 2008). Thus, I consider pyramidal cells and GABAergic interneurons as 'cell classes'. Furthermore, I divide interneurons innervating the dendrites of CA1 pyramidal cells into four cell groups according to their expression of parvalbumin (PV), cholecystokinin (CCK), axonal arborization density and long-range projections. Overall, these four cell groups contain

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12 distinct cell types. Different cell types can usually not be discriminated on the basis of a single characteristic but by a combination of several characteristics. It should be noted that basket cells, which are not discussed here, innervate not only somata but also dendrites of pyramidal cells; the exact proximity of this dendritic innervation to the somata is variable and not well defined.

Parvalbumin-expressing interneurons targeting dendrites of pyramidal cells

O-LM cells (no. 1, Fig. 1)

The eponymous axonal arborization and dendritic orientations of oriens lacunosum-moleculare (O-LM) cells are striking features that make them easily recognizable and arguably the most studied interneurons that target dendrites of pyramidal cells. In the CA1 area, O-LM cells are located in stratum oriens and have horizontally extending dendrites with hairy spines on distal segments. The axons of O-LM cells give few collaterals in stratum oriens but project mainly through the strata pyramidale and radiatum to branch heavily in stratum lacunosum-moleculare (Ramon y Cajal, 1893; McBain *et al.*, 1994; Sik *et al.*, 1995; Maccaferri & McBain, 1996), matching the glutamatergic input from the entorhinal cortex and thalamus. The axons give some collaterals also in the deep stratum radiatum but do not cross the fissure to the dentate gyrus (Fig. 2F). The main glutamatergic input to O-LM cells arises from local CA1 pyramidal cells (Blasco-Ibanez & Freund, 1995) and O-LM cells in turn project to the apical tuft of CA1 pyramidal cells and other interneurons (Katona *et al.*, 1999a; Maccaferri *et al.*, 2000). Therefore, O-LM cells are often regarded as a classical example of GABAergic feedback inhibition. O-LM cells express the neuropeptide somatostatin (Naus *et al.*, 1988; Baude *et al.*, 1993; Maccaferri *et al.*, 2000; Klausberger *et al.*, 2003), high levels of mGluR1α (Baude *et al.*, 1993), lower levels of the Ca^{2+}-binding protein parvalbumin as compared with basket cells (Klausberger *et al.*, 2003; Ferraguti *et al.*, 2004; Tukker *et al.*, 2007), receive glutamatergic and GABAergic input with high levels of mGluR7 (Shigemoto *et al.*, 1996; Somogyi *et al.*, 2003), and receive GABAergic input from vasoactive intestinal peptide-expressing interneurons (Acsady *et al.*, 1996; Hajos *et al.*, 1996). None of these molecules is expressed uniquely by or in the inputs of O-LM cells; however, the combination of several of the above markers together may define O-LM cells. The input–output relationship of

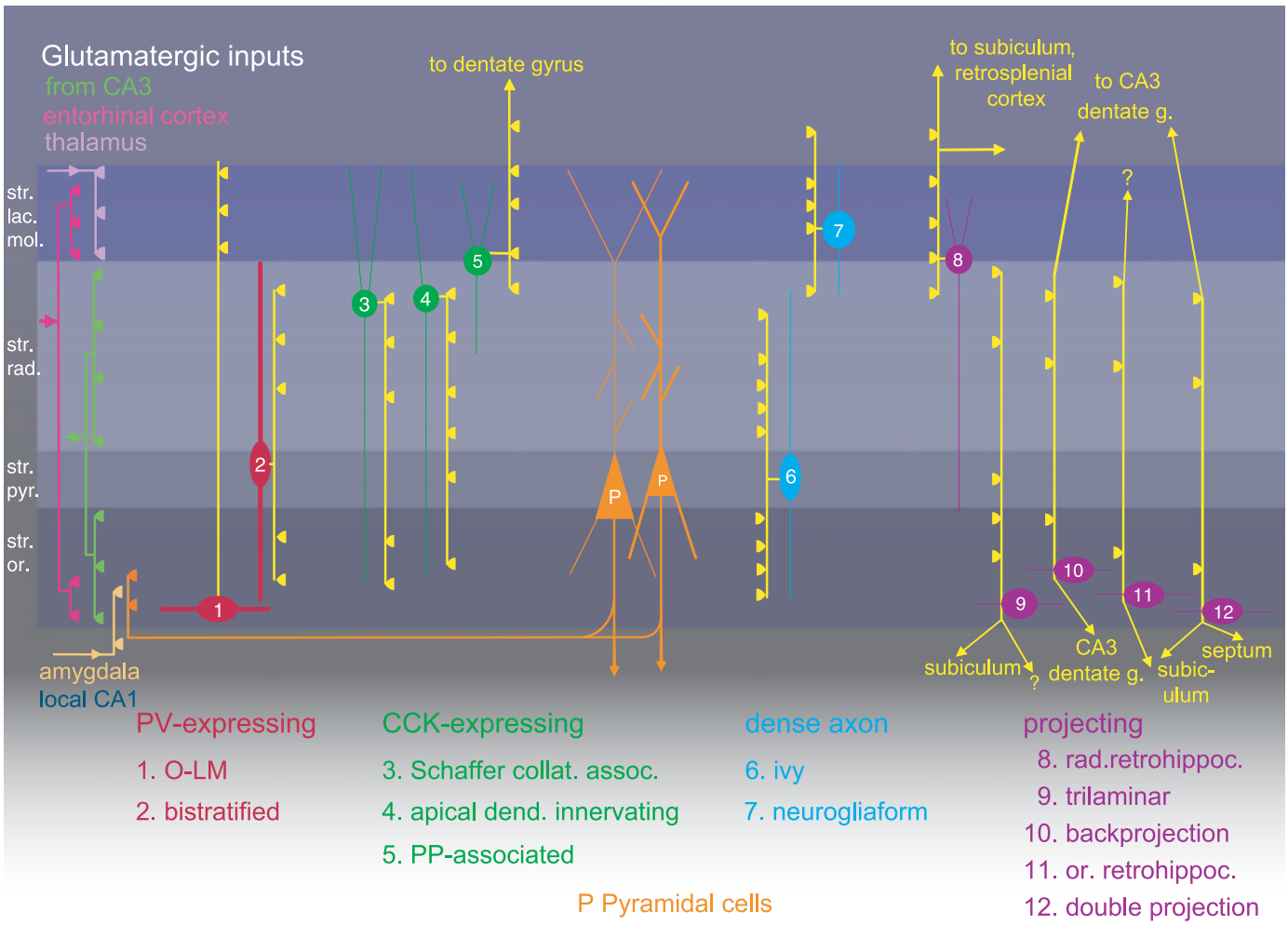

FIG. 1. At least 12 types of GABAergic interneuron divided into four cell groups innervate dendrites of CA1 pyramidal cells. The main termination of five glutamatergic inputs are indicated on the left. The somata and dendrites of interneurons innervating pyramidal cell (orange) dendrites are coloured according to four cell groups. Axons and the main synaptic terminations are yellow. Note the association of the output synapses of different interneuron types with either the Schaffer collateral/commissural or the entorhinal pathway termination zones. Abbreviations: str., stratum; lac. mol., lacunosum moleculare; pyr., pyramidale; or., oriens; g., gyrus; O-LM, oriens lacunosum-moleculare; PP, perforant path; retrohippoc., retrohippocampal projecting.

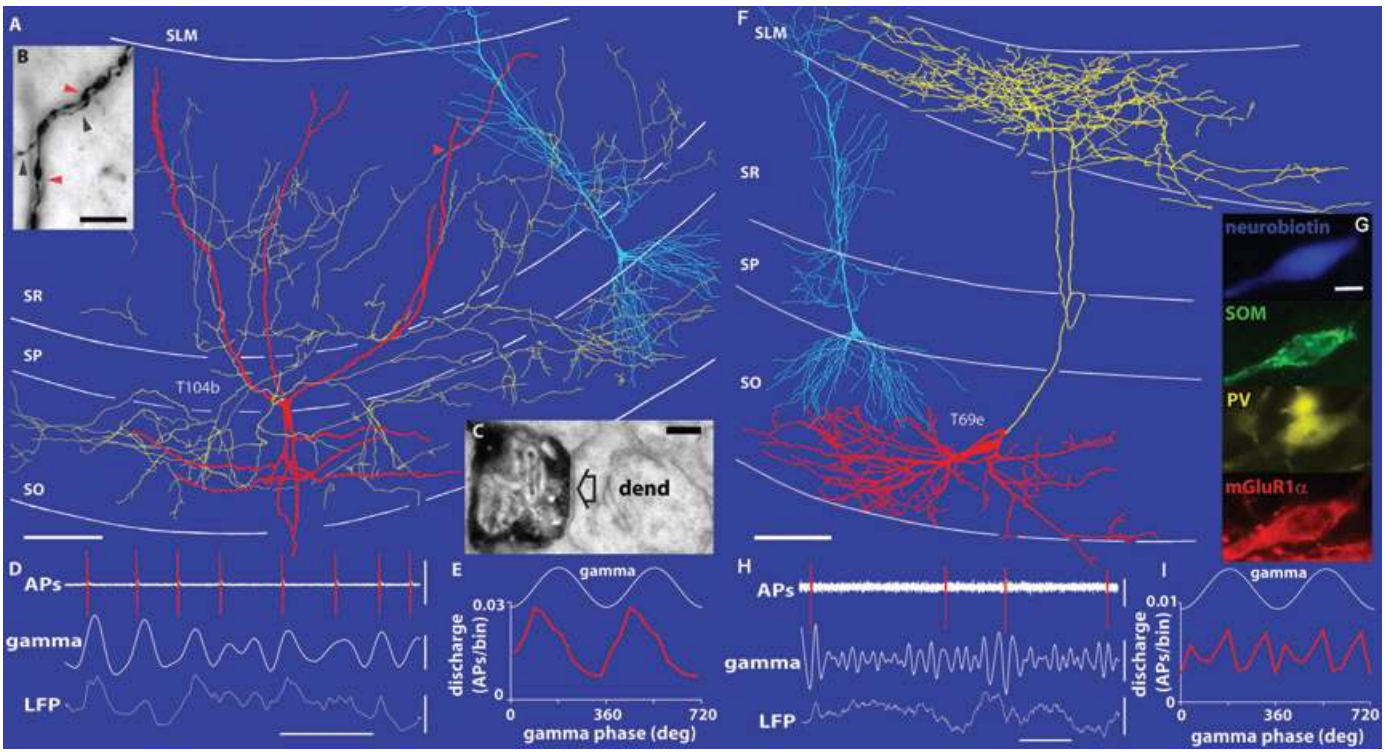

FIG. 2. Distinct spike timing of a bistratified and an O-LM interneuron during gamma oscillations. (A) Reconstruction of the neurobiotin-labelled soma and dendrites (red; shown complete) and axons (yellow; shown from only five 70-μm-thick sections). A pyramidal cell is superimposed in blue for orientation (different scale and animal). (B) Light micrograph of putative dendritic self-innervation sites (red arrow in A). Black and red arrowheads mark axon and dendrite, respectively. (C) Electron micrograph showing a terminal of the same bistratified cell (black) making a type 2 synapse (arrow) with an oblique pyramidal dendrite (dend). (D) Extracellularly recorded action potentials (APs, top) and local field potentials (LFP, bottom, recorded extracellularly with a second electrode in SP) with filtered gamma oscillations (bandpass 30–80 Hz; middle). The bistratified cell fires preferentially at the ascending gamma phase. (E) Average discharge rates as a function of gamma phase (per 36° bin; two cycles are shown with troughs at 0°, 360° and 720°). (F) Reconstructions of the neurobiotin-labelled somata and dendrites (red; shown complete) and axons (yellow; shown from only 12 70-μm-thick sections). (G) The neurobiotin-labelled O-LM cell is immunopositive for PV, somatostatin and mGluR1α. (H) Extracellularly recorded action potentials (APs, top) and local field potentials (LFP, bottom, recorded extracellularly with a second electrode in SP) with filtered gamma oscillations (bandpass 30–80 Hz; middle). The O-LM cell firing is not coupled to any particular gamma phase. (I) Average discharge rates as a function of gamma phase (per 36° bin; two cycles are shown). SLM, stratum lacunosum moleculare; SR, stratum radiatum; SP, stratum pyramidale; SO, stratum oriens. Scale bars: A, 100 μm; B, 10 μm; C, 0.2 μm; D, horizontal 0.05 s; vertical from top to bottom 2 mV, 0.2 mV, 0.2 mV; F, 100 μm; G, 10 μm; H, horizontal 0.1 s; vertical from top to bottom 0.2 mV, 0.1 mV, 0.4 mV. Reproduced, with permission, from Tukker *et al.* (2007).

O-LM cells has recently be reviewed in detail (Maccaferri, 2005); most remarkable is the facilitating nature of the excitatory synapses onto O-LM cells from CA1 pyramidal cells (Ali & Thomson, 1998; Losonczy *et al.*, 2002; Biro *et al.*, 2005).

Bistratified cells (no. 2, Fig. 1)

The axonal arborization of bistratified cells (Buhl *et al.*, 1994; Pawelzik *et al.*, 1997) overlaps with the glutamatergic input from CA3 pyramidal cells in stratum radiatum and oriens (Fig. 2A). This two-layered axonal arrangement gives the cell its name. Bistratified cells make GABAergic synapses with basal and oblique dendrites of CA1 pyramidal cells (Buhl *et al.*, 1994; Maccaferri *et al.*, 2000; Pawelzik *et al.*, 2002; Klausberger *et al.*, 2004). Their somata are mainly located in stratum pyramidale, but oriens-bistratified cells with somata and horizontally running dendrites in stratum oriens have also been reported (Maccaferri *et al.*, 2000). The dendrites of bistratified cells in stratum pyramidale extend widely in the strata oriens and radiatum and form connexin36-containing gap junctions with other interneurons (Baude *et al.*, 2007). In contrast to basket and axo-axonic cells, the dendrites of bistratified cells do not enter stratum lacunosum-moleculare but often bend back at the radiatum/lacunosum-moleculare border (Fig. 2A). Bistratified cells express PV in their soma and dendrites to a similar extent to basket and axo-axonic cells, they also express somatostatin and neuropeptide Y, and their extrasynaptic membrane is highly enriched in $GABA_A$ receptors containing the α1 subunit (Pawelzik *et al.*, 2002; Klausberger *et al.*, 2004; Baude *et al.*, 2007). Noted that at least one type of GABAergic projection neuron expresses also a low level of PV; however, these neurons are included in the group of GABAergic projecting cells.

CCK-expressing interneurons targeting pyramidal cell dendrites

In contrast to the well-established interneuron types of O-LM and bistratified cells, only few CCK-expressing interneurons targeting dendrites of pyramidal cells have been evaluated in detail.

Schaffer collateral-associated cells (no. 3, Fig. 1)

The somata of Schaffer collateral-associated cells are located mainly in stratum radiatum with dendrites spanning all layers. The axons of these cells innervate the oblique and to a lesser extent basal dendrites of CA1 pyramidal cells and interneurons in stratum radiatum and oriens, matching the excitatory input from CA3 pyramidal cells, giving the cell its name. In contrast to bistratified cells, the axons of Schaffer collateral associated cells are concentrated more in stratum

radiatum than in stratum oriens (Cossart *et al.*, 1998; Vida *et al.*, 1998; Cope *et al.*, 2002; Pawelzik *et al.*, 2002). Some Schaffer collateral-associated cells express CCK (Pawelzik *et al.*, 2002) and the Ca^{2+}-expressing protein calbindin (Cope *et al.*, 2002). It is likely that the axons of these cells are immunopositive for cannabinoid CB1 receptors; however, this has yet to be demonstrated directly.

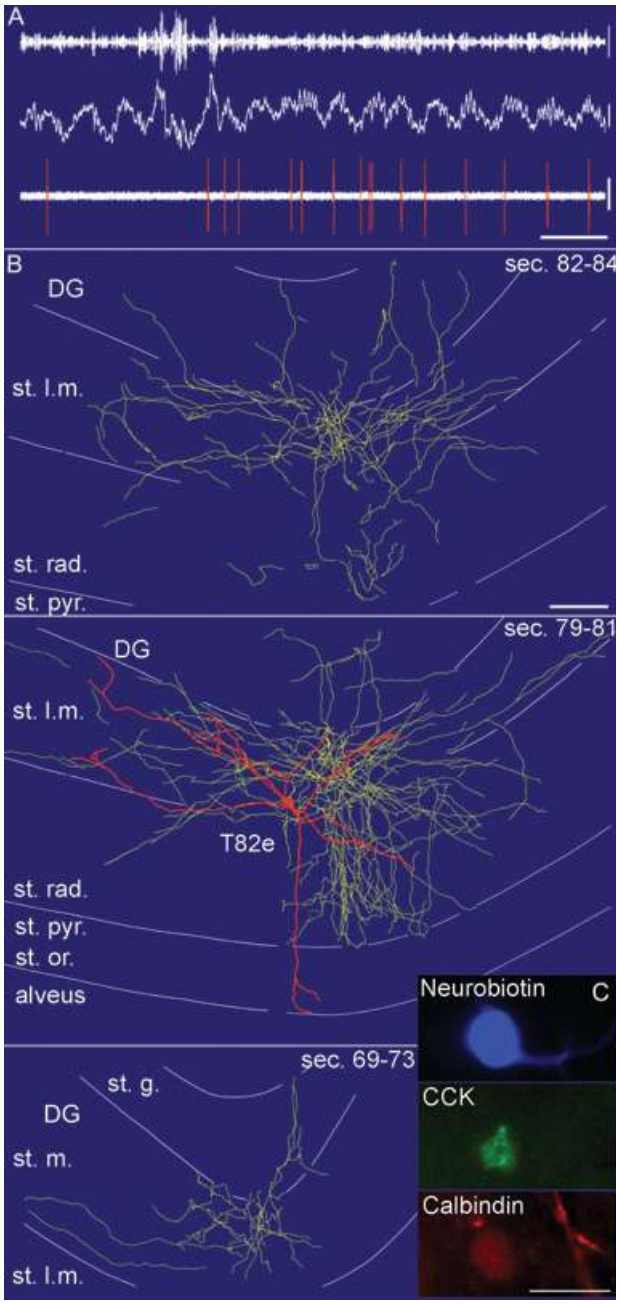

FIG. 3. *In vivo* firing patterns and visualization of a CCK-expressing perforant-path-associated cell. (A) *In vivo* firing patterns of the cell. Note that during the initial ripple episodes the cell did not fire but became active during the subsequent theta oscillations, when it fired at the ascending phase of the theta waves recorded in the stratum pyramidale with a second electrode. Scale bars, 0.2 s; lfp and spikes 0.5 mV; ripples 0.1 mV. (B) Reconstruction of the soma and dendrites (orange) is shown complete; the axon (yellow) is shown from selected series of sections as indicated (lower section number marks more caudal position). DG, dentate gyrus; st. m., stratum moleculare; st. g., stratum granulosum. Scale bar (same for all three projections), 100 μm. (C) Immunofluorescence micrograph of the neurobiotin-labelled cell (blue), CCK (green) and calbindin (red) immunoreactivity. Scale bar, 20 μm. Reproduced, with permission, from Klausberger *et al.* (2005).

Apical dendrite innervating cells (no. 4, Fig. 1)

The somata, dendritic and axonal distributions of apical dendrite innervating cells are very similar to those of Schaffer collateral-associated cells. However, electron microscopic investigations have indicated that the apical dendrite-targeting cells innervate preferentially the main apical shaft of CA1 pyramidal cells (Klausberger *et al.*, 2005), in contrast to Schaffer collateral-associated cells, which target the oblique and basal dendrites of pyramidal cells. Apical dendrite innervating cells express CCK and one *in vivo* labelled cell was shown to be immunopositive for CB1 receptor, the vesicular glutamate transporter VGLUT3 and the neurokinin-1 receptor (Klausberger *et al.*, 2005).

Perforant path-associated cells (no. 5, Fig. 1)

The cell bodies of perforant path-associated cells (Fig. 3) are often located at the stratum radiatum/lacunosum moleculare border and their dendrites can either cover all layers or remain in stratum lacunosum moleculare and adjacent stratum radiatum. The axons of this cell type are concentrated in stratum lacunosum moleculare, overlapping with the excitatory perforant path input from the entorhinal cortex, giving the cell its name (Hajos & Mody, 1997; Cossart *et al.*, 1998; Vida *et al.*, 1998; Pawelzik *et al.*, 2002; Klausberger *et al.*, 2005). Thus, the axons of both O-LM and perforant path-associated cells innervate the apical tuft of CA1 pyramidal cells. Interestingly, whereas the axons of O-LM cells always remain within the CA1 area, the axons of perforant path-associated cells (Fig. 3) often cross the fissure and also innervate the dendrites of granule cells in the dentate gyrus (Klausberger *et al.*, 2005), and hence their name. The CA1 area and the dentate gyrus receive input from distinct layers of the entorhinal cortex. The consequences of axons of O-LM cells converging only with input from layer 3 entorhinal pyramidal cells in CA1 and axons from perforant path-associated cells overlapping with layer 2 and 3 entorhinal input in CA1 and dentate gyrus remain unexplored. At least some perforant path-associated cells express CCK (Pawelzik *et al.*, 2002) and one *in vivo* labelled cell tested positive for calbindin, and another tested positive for CB1 receptor (Klausberger *et al.*, 2005).

Interneurons with densely packed axons

Densely packed axon interneurons share not only a peculiar axonal cloud but also evoke slow responses in pyramidal cells.

Neurogliaform cells (no. 6, Fig. 1)

The cell bodies of neurogliaform cells are often located in stratum lacunosum moleculare and they have relatively short and numerous dendrites, giving the cell its name (Khazipov *et al.*, 1995; Vida *et al.*, 1998; Price *et al.*, 2005, 2008; Zsiros & Maccaferri, 2005). The axons of neurogliaform cells are extremely dense in stratum lacunosum moleculare; however, a quantitative measure for this axonal arborization remains to be established. Similar to CCK-expressing perforant path-associated cells but in contrast to O-LM cells, the axons of neurogliaform cells often cross the fissure into the dentate gyrus. Many neurogliaform cells express neuropeptide Y and α-actinin-2 (Ratzliff & Soltesz, 2001; Price *et al.*, 2005) and are connected by gap junctions and GABAergic synapses (Price *et al.*, 2005; Zsiros & Maccaferri, 2005). Compared with other interneurons, neurogliaform

cells evoke slower $GABA_A$ receptor and also $GABA_B$ receptor-mediated responses in CA1 pyramidal cells (Price *et al.*, 2005, 2008), similar to neurogliaform cells in the neocortex (Tamas *et al.*, 2003).

Ivy cells (no. 7. Fig. 1)

In contrast to neurogliaform cells innervating the apical tuft of pyramidal cells, the very dense axons of ivy cells (Fig. 4), resembling the thick branching of this plant, cover stratum oriens and radiatum, making synapses onto the basal and oblique dendrites of pyramidal cells (Fuentealba *et al.*, 2008; Szabadics & Soltesz, 2009). The cell bodies of ivy cells are located in stratum pyramidale and radiatum and the usually short dendrites can cover all layers. Ivy cells express neuropeptide Y (Fuentealba *et al.*, 2008; Szabadics & Soltesz, 2009), neuronal nitric oxide synthase and a high level of $GABA_A$ receptor containing the α1 subunit (Fuentealba *et al.*, 2008). Based on this expression profile it was estimated that ivy cells might represent the most numerous GABAergic cell type in the CA1 area. Similar to neurogliaform cells, ivy cells evoke slow GABAergic responses in CA1 pyramidal cells, possibly caused by extrasynaptic transmitter release by the ivy cells and distinct post-synaptic receptor subtypes. In the extremely dense axonal cloud of ivy cells, vesicles have been observed far from synaptic specializations, suggesting possible

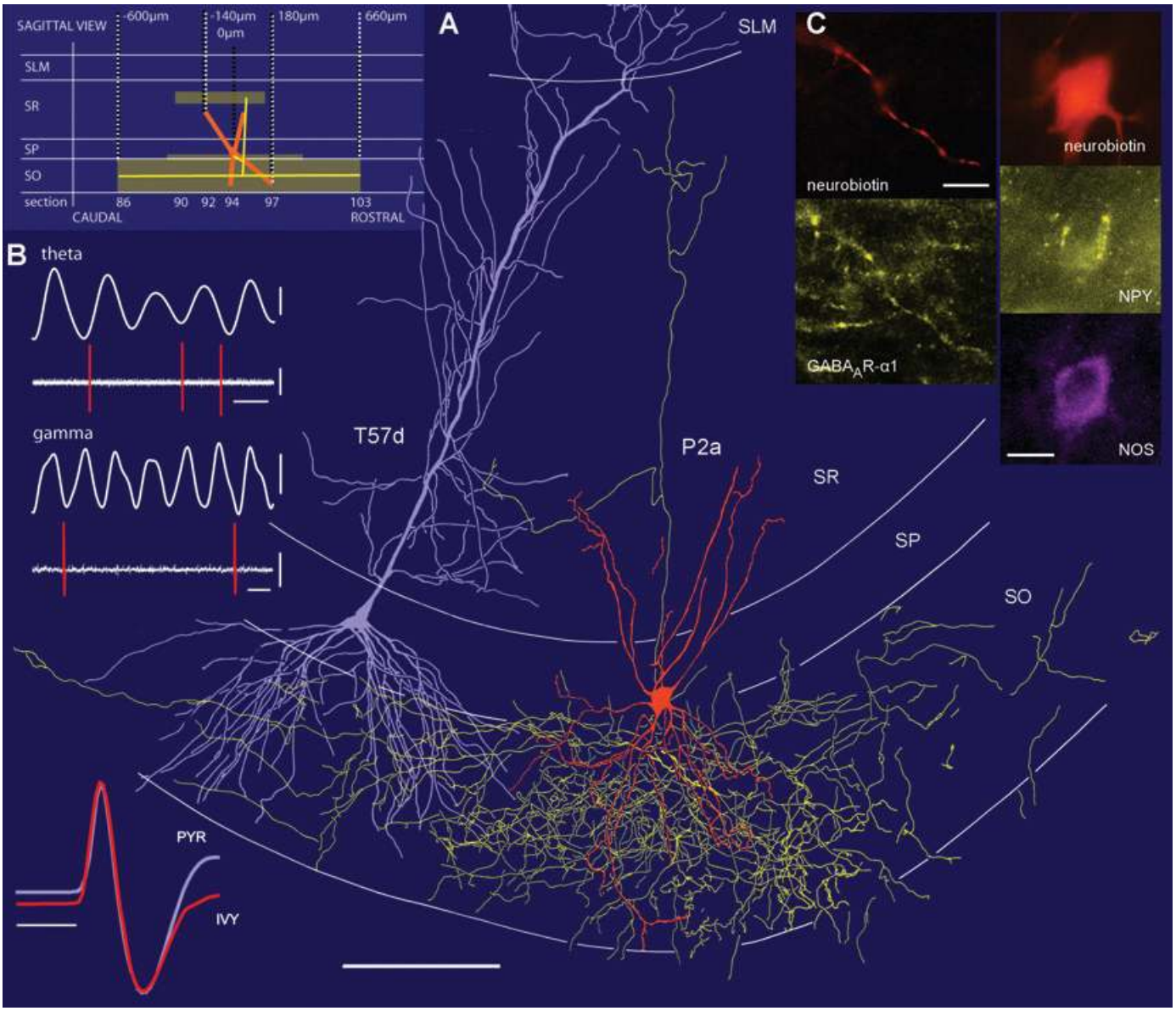

FIG. 4. Firing patterns, molecular characteristics and spatial distribution of an ivy cell recorded *in vivo*. (A) Schematic sagittal view (top left) of the axonal (yellow) and dendritic (orange) fields and reconstruction in the coronal plane of a neurobiotin-labelled ivy cell (P2a). The soma and dendrites are shown from all sections; the axon is presented only from three 70-μm-thick sections for clarity. Note the very dense axon in stratum oriens. A pyramidal cell (T57d, blue) recorded and labelled in another animal is added to illustrate spatial relationships. Bottom left, scaled superimposed extracellular action potential waveform averages from the ivy (orange) and pyramidal (blue) cell. Note the similar shape and time course of the waveforms. (B) The ivy cell discharged sparsely but phase-locked to the trough of the extracellularly recorded theta (filtered 3–6 Hz, top) and gamma (filtered 30–80 Hz, bottom) oscillations in stratum pyramidale. (C) Fluorescence micrographs showing immunoreactivity for neuronal nitric oxide synthase and neuropeptide Y in the soma, and for the α1 subunit of the $GABA_A$ receptor in a dendrite. Scale bars (A) 100 μm; 1 ms; (B) filtered 0.2 mV, units 0.5 mV, theta 200 ms, gamma 20 ms; (C) 10 μm. Reproduced, with permission, from Fuentealba *et al.* (2008).

extrasynaptic transmitter release. Extrasynaptically released GABA, neuropeptide Y and nitric oxide might modulate not only post-synaptic pyramidal cell dendrites but also terminals innervating pyramidal cell dendrites via presynaptic receptors.

GABAergic long-range projecting neurons

In the hippocampus there are GABAergic neurons that are not local interneurons but send long-range projections with myelinated axons to other brain areas. Their local axon innervates the dendrites of CA1 pyramidal cells together with local GABAergic interneurons. These peculiar GABAergic neurons have not been studied extensively and therefore the different cell types are not well defined.

Radiatum retrohippocampal projection neurons (no. 8, Fig. 1)

The somata of the radiatum retrohippocampal projection neurons (Jinno *et al.*, 2007; Tomioka & Rockland, 2007) are located in deep stratum radiatum or lacunosum moleculare and they have a sparse local axonal arborization in the same areas. Remarkably, these cells send long-range projections with thick myelinated axons to the subiculum, presubiculum, retrosplenial cortex and, as reported on at least one occasion, also to the indusium griseum. The molecular expression profile of these cells remains to be established.

Trilaminar cells (no. 9, Fig. 1)

Trilaminar cell (Sik *et al.*, 1995; Ferraguti *et al.*, 2005) somata are located in the stratum oriens with horizontally running dendrites. It should be noted that this distinct cell type is not simply defined by axonal arborizations in three layers (strata oriens, pyramidale and radiatum), because many other distinct interneurons innervate the same layers. Trilaminar cells not only innervate the dendrites but also to a lesser extent the somata of CA1 pyramidal cells. They project to the subiculum, are strongly immunopositive for the muscarinic M2 receptor and receive dense mGluR8a decorated input on their somata and dendrites; furthermore, trilaminar cells can fire with high-frequency bursts in contrast to most GABAergic interneurons.

Backprojecting cells (no. 10, Fig. 1)

Backprojecting cells (Sik *et al.*, 1994) are located in stratum oriens with horizontally running dendrites. Their axons innervate different layers of the CA1 area, and main axons cross the fissure and extensively project backwards to other hippocampal subfields including CA3 and dentate gyrus. Backprojecting cells express somatostatin (Goldin *et al.*, 2007).

Oriens retrohippocampal projection cells (no. 11, Fig. 1)

The somata and horizontally running dendrites of oriens retrohippocampal projection cells are located in stratum oriens. The local axons innervate mainly dendrites of CA1 pyramidal cells and main axons project via the white matter to the subiculum and retrohippocampal areas (Jinno *et al.*, 2007). *In vivo* labelled and retrogradely filled cells are heterogeneous in their molecular expression and therefore it cannot be excluded that oriens retrohippocampal projection cells comprise more than one type.

Double projection cells (no. 12, Fig. 1)

Retrograde and anterograde tracing have revealed GABAergic neurons that project to the medial septum (Alonso & Kohler, 1982; Gulyas *et al.*, 1993; Toth *et al.*, 1993; Zappone & Sloviter, 2001; Jinno & Kosaka, 2002). *In vivo* labelling of septal-projecting GABAergic cells and comparison of immunoreactivity in neurons retrogradelly labelled from the septum or subiculum have suggested that the vast majority of hippocampo-septal cells also project to the subiculum (Jinno *et al.*, 2007). This double area long-range projection gives the cell its name. The cell bodies of these cells and the horizontally running dendrites are located in stratum oriens. The local axons in CA1 innervate mainly dendrites of pyramidal cells (Jinno *et al.*, 2007; Takács *et al.*, 2008). However, another study reported a preferential innervation of CA1 interneurons by the local axons of hippocampo-septal cells (Gulyas *et al.*, 2003) and it remains to be established if the latter data derived from an additional cell type. The majority of double projection cells express somatostatin and calbindin; neuropeptide Y and M2 receptor are expressed by some double projection cells; and one *in vivo* labelled double projection cell was weakly immunopositive for PV. It cannot be excluded that double projection cells comprise several types or subtypes.

Spike timing of dendrite-targeting interneurons during hippocampal network oscillations *in vivo*

The concerted and synchronous activities of neurons in a layered structure such as the CA1 hippocampus are reflected by network oscillations in the extracellular field potential (Buzsaki & Draguhn, 2004). The rhythmic activity of neurons allows a temporally structured processing of information and supports the formation and reactivation of cell assemblies (Buzsaki, 2006). The frequency of the brain oscillations strongly correlates with ongoing behaviour. Theta oscillations (4–12 Hz) represent the on-line state of the hippocampus and occur during navigation, learning, and memory formation and retrieval, and during rapid-eye-movement sleep (Vanderwolf, 1969). Ripple oscillations (120–200 Hz) occur during resting and consummatory behaviours as well as during sleep and contribute to the replay and consolidation of memories (O'Keefe, 1978; Buzsaki, 1989; Foster & Wilson, 2006; Diba & Buzsaki, 2007). Gamma oscillations (30–80 Hz) occur during all behavioural states, together with and modulated by theta oscillations, and are thought to provide temporal frames for the binding and processing of information (Gray & Singer, 1989; Csicsvari *et al.*, 2003). The cellular mechanisms for the generation and maintenance of network oscillations is currently of major interest and GABAergic interneurons are considered as major contributors to the synchrony of pyramidal cell activity (Maier *et al.*, 2003; Whittington & Traub, 2003; Gloveli *et al.*, 2005; Mann *et al.*, 2005; Behrens *et al.*, 2007; Fuchs *et al.*, 2007; Cardin *et al.*, 2009). Interneurons targeting the soma and axon initial segment of pyramidal cells almost certainly contribute to network oscillations but what is the role of dendrite-targeting interneurons in rhythmic brain activities?

Division of labour between distinct dendrite-targeting interneurons during gamma oscillations

Different types of dendrite-targeting interneurons, as defined by their synaptic connectivity and molecular expression profile, exhibit distinct firing patterns during various network oscillations in the hippocampus of anaesthetized rats. This is exemplified by the distinct spike timing of O-LM and bistratified cells during gamma oscillations, as illustrated in Fig. 2 (Tukker *et al.*, 2007). Both cell types are active during

gamma oscillations. However, only the spike timing of bistratified cells is strongly coupled to the gamma oscillations recorded as the extracellular local field potential. In contrast, O-LM cells fire without preference on all phases of the field gamma oscillations. The basal and oblique dendrites of pyramidal cells, also receiving glutamatergic input from the CA3 area, are modulated to field gamma oscillations by bistratified cells, while the apical tuft which also receives glutamatergic input from the entorhinal cortex is not synchronized to field gamma oscillations by O-LM cells. Interestingly, the spike timing of bistratified cells is most strongly coupled to field gamma oscillations, stronger even than the gamma coupling of basket and axo-axonic cells (Penttonen *et al.*, 1998; Tukker *et al.*, 2007). One might argue that this is purely a consequence of the dendritic geometry of bistratified cells, which receive gamma-modulated excitatory input only from CA3 and CA1 pyramidal cells but not from the entorhinal cortex. Bistratified cell output might not strongly affect the output of post-synaptic pyramidal cells, because the amplitude and timing of postsynaptic potentials evoked by bistratified cells is smaller and less precise in comparison with those evoked by basket and axo-axonic cells when detected at the pyramidal cell soma. However, such an argument focuses only on the linear summation of all responses at the soma or initial segment and disregards the possibility of local dendritic computations, as demonstrated recently (Losonczy *et al.*, 2008). Bistratified cells target mainly basal and oblique dendrites rather than main apical dendrites. Therefore, the frequently and well-timed firing of bistratified cells may induce intracellular gamma oscillations in these small dendrites, which are strongly coupled to the gamma oscillations in the field. Incoming excitation and back- or forward-propagating spikes in these dendrites will be scaled according to population gamma phase via the bistratified cells.

Ivy cells, which evoke slower GABAergic responses in the basal and oblique dendrites of pyramidal cells, also fire phase-coupled to field gamma oscillations (Fuentealba *et al.*, 2008). Because these cells fire with lower frequency than bistratified cells (Klausberger *et al.*, 2004; Fuentealba *et al.*, 2008), it is possible that the slower inhibitory post-synaptic potentials caused by the occasional action potentials of ivy cells disrupt the coupling between the intracellular dendritic and extracellular field gamma oscillations. In contrast, the firing of CCK-expressing interneurons are only weakly coupled to field gamma oscillations (Tukker *et al.*, 2007). Furthermore, they fire significantly earlier during the gamma cycle than other interneurons and in time to set a threshold for the firing of pyramidal cells. Because of the CB1 receptor expression of CCK terminals (Katona *et al.*, 1999b), the few active pyramidal cells can block this threshold-lowering GABAergic signal in their own input from CCK-expressing interneurons, resulting in a winner-takes-all effect and sparse coding of CA1 pyramidal cells.

All types of interneuron innervating apical tufts of pyramidal cells in lacunosum-moleculare reduce firing during ripple oscillations

Although there are major differences in the firing patterns of interneuron types from different groups innervating the same dendritic compartment during other network oscillations, there is an astonishing harmony of all interneuron types innervating the apical tuft of pyramidal cells during sharp wave-associated ripple oscillations (Fig. 5): O-LM (Klausberger *et al.*, 2003), CCK-expressing perforant path-associated (Klausberger *et al.*, 2005) and radiatum retrohippocampal projecting cells (Jinno *et al.*, 2007) all reduce their firing during ripple oscillations (for the neurogliaform cells no published data are available at this time). This is remarkable because the apical tuft of pyramidal cells in stratum lacunosum-moleculare, receiving excitatory input from the entorhinal cortex and thalamus, has not been a major subject of investigation in connection to sharp wave-associated ripples. Ripples in the CA1 area are generated by strong excitatory input from CA3 pyramidal cells innervating the basal and oblique CA1 pyramidal cell dendrites in strata oriens and radiatum (Csicsvari *et al.*, 2000). The activity of layer 3 principal cells in the entorhinal cortex projecting to CA1 stratum lacunosum-moleculare during ripple oscillations in the CA1 hippocampus has not yet been determined. It has been suggested (Klausberger *et al.*, 2003) that the reduction of GABAergic inputs from all sources in the lacunosum-moleculare allows the back-propagation of action potentials (Spruston *et al.*, 1995; Markram *et al.*, 1997) all the way to the apical tuft of CA1 pyramidal cells. This would result in potentiating those synapses from the entorhinal cortex that are active during CA1 ripple oscillations. In such a scenario, sharp wave-associated ripples would not only provide a read-out of hippocampal cell assemblies to the isocortex (Buzsaki, 1989), but would also strengthen the simultaneously active dendritic inputs to the CA1 cell assemblies from the entorhinal cortex.

The strong excitatory input from CA3 pyramidal cells to the basal and oblique dendrites of CA1 pyramidal cells during sharp wave-associated ripples (Csicsvari *et al.*, 2000) is accompanied by a strong GABAergic input from the bistratified cells to the same dendritic compartments (Klausberger *et al.*, 2004). A closer inspection of the spike timing during single ripple cycles indicated that bistratified cells fire phase-coupled to field ripple oscillations and shortly after the pyramidal cells discharge. Therefore, bistratified cells might not primarily inhibit the dendrites of pyramidal cells during ripples, but rather contribute to the de-inactivation of voltage-gated ion channels following discharge and promote consecutive firing. It is not clear if the precisely coupled firing of bistratified cells to field ripple oscillations can generate a fast intracellular oscillation in the pyramidal cell dendrites. This would require a fast recovery from the inhibitory input within a few milliseconds, which is only possible with a very fast time constant of the dendritic membrane. However, the membrane conductance of basal and oblique dendrites during ripple oscillations remains unknown.

The long-range projecting neurons (Fig. 5) that also innervate the basal and oblique dendrites of pyramidal cells in strata oriens and radiatum (trilaminar cell, oriens retrohippocampal projecting cell, double projecting cell) discharge with firing patterns similar to bistratified cells during ripple oscillations (Jinno *et al.*, 2007). By contrast, CCK-expressing apical dendrite-targeting cells and ivy cells, in general, did not change their firing rate during ripple events, possibly reflecting their integrated excitatory and inhibitory inputs. Therefore, these cells might contribute to the input-selection of active pyramidal cell assemblies during sharp waves, in contrast to bistratified and long-range projecting neurons, which provide universal temporal modulation.

Theta oscillations

During theta oscillations most interneurons targeting pyramidal cell dendrites fire around the trough (Fig. 5) of extracellular field theta oscillations measured in the pyramidal cell layer (Klausberger *et al.*, 2003, 2004; Ferraguti *et al.*, 2005; Jinno *et al.*, 2007; Fuentealba *et al.*, 2008). This is at the same phase when CA1 pyramidal cells are most active. Therefore, dendritic GABAergic input to pyramidal cells does not provide the inhibition for the ‘silent’ phase of the theta cycle but

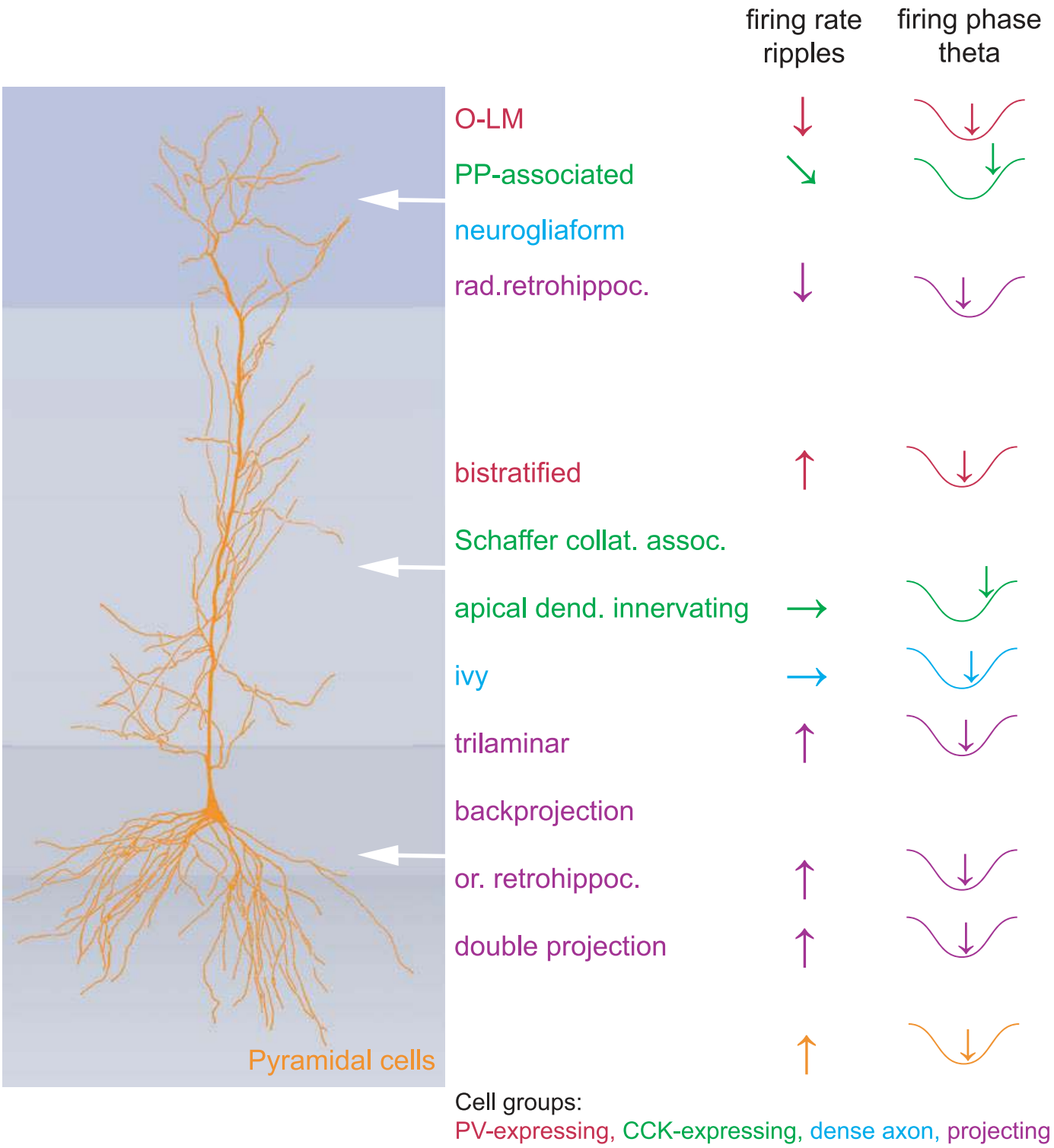

FIG. 5. Distinct types of interneurons exhibit differential spike timing during network oscillations *in vivo*. Different interneuron types are displayed to innervate either the apical tuft or the basal and oblique dendrites and the colour indicates the cell group. Upward- and downward-pointing arrows indicate an increase and decrease, respectively, of firing rate during ripple oscillations. Arrows in the schematic theta cycle indicate the preferred spike timing during extracellular theta oscillations recorded in the CA1 pyramidal cell layer.

rather modulates and scales excitatory input when pyramidal cells are most active.

In contrast to other interneurons in the CA1 area, CCK-expressing cells fire at the ascending phase of extracellular field theta oscillations measured in the pyramidal cell layer (Klausberger *et al.*, 2005), when phase-precessing pyramidal place cells start firing (O'Keefe & Recce, 1993). Because active place cells might block the GABAergic input from CCK-expressing interneurons via CB1 receptors, CCK-express-

ing dendrite-targeting interneurons might contribute to the sparse place coding in the CA1 hippocampus (Freund *et al.*, 2003; Klausberger *et al.*, 2005).

Open questions about dendritic GABAergic input

How many types of interneuron targeting the dendrites of pyramidal cells are in the CA1 area of the hippocampus?

I have grouped dendrite-targeting interneurons into groups and types in analogy to the classification of neurons proposed by Bota & Swanson (2007). It is likely that ongoing and future investigations will reveal additional types of interneuron, some types may be split into subtypes or other types may be merged. Gene expression atlases (http://www.brain-map.org) and large-scale molecular expression profiles of cells will contribute to advances in classification (Sugino *et al.*, 2006). Only a complete ontogenetic dataset will define a tree of relationships between different GABAergic interneurons. However, to understand the contribution of different interneurons to circuit operations it is necessary to reveal their synaptic inputs and outputs and the timing of their activity in relation to connected circuits.

How does the specificity in dendritic and axonal arborizations develop?

Axonal and dendritic arborizations define cell types that also show homogeneous spike timing during network oscillations *in vivo*. But the molecular signals that govern this target specificity of inputs and outputs remain to be discovered.

Which $GABA_A$ receptor subtypes and neuropeptide receptors are activated by distinct interneuron types?

Interneurons mediate their synaptic responses mainly via $GABA_A$ receptors. Depending on the subunit composition of these hetero-oligomeric receptors, there is a large diversity of different $GABA_A$ receptor subtypes with distinct pharmacology (Sieghart & Sperk, 2002). This opens the possibility that different interneuron types targeting the dendrites of CA1 pyramidal cells could act on distinct receptor subtypes (Pawelzik *et al.*, 1999; Thomson *et al.*, 2000). For example, densely packed axon interneurons evoke slow $GABA_A$ receptor-mediated responses in CA1 pyramidal cells (Fuentealba *et al.*, 2008; Price *et al.*, 2008) and $GABA_A$ receptors containing the $\alpha 5$ subunit contribute to slow $GABA_A$ receptor-mediated inhibition (Zarnowska *et al.*, 2009), but a direct connection between these two observations has not yet been documented.

Interneurons not only release GABA but are also a major source for neuropeptides in the hippocampus. How these neuropeptides contribute to dendritic processing of pyramidal cells remains difficult to establish, because the activity of interneurons causing neuropeptide release, the subcellular location of most neuropeptide receptors as well as the consequences of neuropeptide receptor activation to dendritic operations *in vivo* all require further work (Baraban & Tallent, 2004).

Does each CA1 pyramidal cell receive input from all types of GABAergic interneuron?

It is not clear whether each CA1 pyramidal cell receives input from all 12 types of interneuron reviewed here. It is possible that certain pyramidal cells receive input only from a subset of interneuron types. This would define different types of pyramidal cells, and it is likely that such pyramidal cell types would contribute differentially to hippocampal network operations.

How do distinct GABAergic inputs regulate dendritic computations in vivo?

It has been suggested that GABAergic input to pyramidal cell dendrites inhibits Ca^{2+} spikes in an *in vitro* preparation (Miles *et al.*, 1996). In the somatosensory cortex it has been shown recently that the strength of sensory stimulation is reflected in a graded dendritic calcium response in pyramidal cells regulated by GABAergic input, putatively deriving from dendrite-targeting interneurons (Murayama *et al.*, 2009). To observe neuronal activity in small pyramidal cell dendrites directly rather than inferring it from somatic or apical dendritic recordings is a prerequisite for the understanding of the GABAergic control of pyramidal cell dendrites. The advent of new imaging techniques has already revealed astonishing detail regarding the computational powers of hippocampal pyramidal cell dendrites (Losonczy & Magee, 2006; Harvey & Svoboda, 2007; Losonczy *et al.*, 2008). However, to understand the contribution of GABAergic input to dendritic processing remains a formidable challenge. *In vitro* preparations allow the testing of possible mechanisms and constraints, but only the full functionality of all synaptic inputs and neuromodulatory controls will provide the framework in which to dissect GABAergic dendritic inputs in the working brain. The timing and causal effects of GABAergic inputs from the 12 distinct sources will have to be monitored in relation to converging excitatory input, action potentials, calcium spikes, neuromodulatory input, coincidence detection and dendritic excitability.

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Abbreviations

CCK, cholecystokinin; O-LM, oriens lacunosum-moleculare; PV, parvalbumin.

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