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REVIEW

Synaptic integration by different dendritic compartments of hippocampal CA1 and CA2 pyramidal neurons

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Abstract Pyramidal neurons have a complex dendritic arbor containing tens of thousands of synapses. In order for the somatic/axonal membrane potential to reach action potential threshold, concurrent activation of multiple excitatory synapses is required. Frequently, instead of a simple algebraic summation of synaptic potentials in the soma, different dendritic compartments contribute to the integration of multiple inputs, thus endowing the neuron with a powerful computational ability. Most pyramidal neurons share common functional properties. However, different and sometimes contrasting dendritic integration rules are also observed. In this review, we focus on the dendritic integration of two neighboring pyramidal neurons in the hippocampus: the well-characterized CA1 and the much less understood CA2. The available data reveal that the dendritic integration of these neurons is markedly different even though they are targeted by common inputs at similar locations along their dendrites. This contrasting dendritic integration results in different routing of information flow and generates different corticohippocampal loops.

Keywords Hippocampus · Dendrite · Synapses · CA1 pyramidal neuron · CA2 pyramidal neurons · Cortical input

The most abundant neuronal type in the cortex, pyramidal neurons were first described by Ramon y Cajal. They are located in most forebrain structures including the cerebral cortex, the hippocampus and the amygdala, but are absent from the midbrain, hindbrain and spinal cord [1]. Pyramidal neurons are present in many species ranging from reptiles to mammals, but not in amphibians [2]. Their emergence during evolution and their location in forebrain structures suggests that they are associated with higher cognitive function.

All pyramidal neurons have a similar structure with a single axon and several short basal dendrites that descend from the base of the soma and a long, large apical dendrite that emerges from the apex of the soma. Many oblique dendrites emanate from the apical dendrite that gives rise to a tuft of dendrites at variable distances from the soma. These dendrites are covered with spines, a postsynaptic differentiation first noticed by Ramon y Cajal in 1888 using Golgi's method [3]. These spines vary greatly in size and shape and serve as the location for most of the excitatory synapses on the dendrites; in contrast, inhibitory synapses are usually located on the soma and the shaft of the dendrite [4].

A typical pyramidal neuron receives tens of thousand of excitatory and inhibitory synaptic inputs [4], with considerable variation in their distance from the site of action potential (AP) generation near the soma. This spatial distribution raises the question as to how synapses located at increasing distances from the soma can control AP output when they are increasingly isolated from the site of AP generation. While this question has puzzled neuroscientists for decades, answers are beginning to emerge thanks to the development of new electrophysiological and optical techniques.

The influence of individual synaptic inputs was initially expected to be very dependent on location on the dendritic axis: distant synapses would have less impact on AP initiation due to the drop in charge from passive current

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propagation along the dendrite. Surprisingly, studies performed in CA1 hippocampal neurons have shown that the amplitude of the excitatory postsynaptic potential (EPSP) evoked by CA3 inputs and recorded at the soma is independent of the site of generation along the apical dendrite [5]. This shows that mechanisms are in place to compensate for the decay in signal due to the location of the synapses on the dendrite. However, this compensation does not hold for all cell types and dendritic compartments. For example, very distal cortical synapses in the molecular layer of CA1 neurons display pronounced attenuation. Interestingly, synapses at the same distal location in CA2 pyramidal [6–8] neurons are capable of generating very large EPSPs [9]. This observation shows that dendritic integration mechanisms vary between compartment and cell type.

In this review, we compare the dendritic morphology of CA1 and CA2 neurons and describe how similar excitatory inputs can have strikingly different impacts on these two neighboring pyramidal neurons. We also address the contribution of inhibitory inputs to controlling excitatory synapses, and describe how differential synaptic integration results in different routing of the information flow within the hippocampus.

Pyramidal cells in the hippocampal circuit

Anatomical considerations: setting the borders between CA3, CA2 and CA1

The structure of the hippocampus has been studied for over a century. Based on Golgi staining techniques, the pyramidal cell layer of the hippocampus was initially divided into two major regions: a region containing pyramidal cells with large cell bodies abutting the dentate gyrus, and a region consisting of pyramidal neurons with smaller cell bodies that extended from it. Originally called regio inferior and regio superior, respectively, by Ramón y Cajal [10], these two regions were further subdivided by Lorente de Nó, who introduced the most commonly used terminology [11]. He defined the regio superior as CA1 and most of the regio inferior as CA3. He defined CA2 as a small zone of cells between CA1 and CA3 that does not receive mossy fiber input from the dentate gyrus. Additionally, he observed that CA2 pyramidal neurons differ from CA3 neurons in that they lack the dendritic thorny excrescences, the postsynaptic differentiation characteristic of mossy fiber synapses [12]. He also defined a CA4 region corresponding to the polymorphic layer of the dentate gyrus, but this area is no longer classified as a separate structure in stereotaxic atlases [13]. Since its initial definition, CA2 has been the subject of substantial controversy, sometimes considered as a separate region and sometimes as an intermingling of cells from CA3 and CA1. However, there is mounting evidence that CA2 pyramidal neurons are both anatomically and functionally different from CA1 and CA3, and the CA2 region is likely larger than Lorente de Nó's initial description.

Several parameters are used to define the boundaries between different hippocampal regions. These include neuronal morphology, the termination zone of afferent inputs, and more recently, the expression of several region-specific proteins. First, from a morphological standpoint, neurons within the initial part of CA3 (CA3a) are more similar to CA2 than to CA3 neurons. For example, branches of the main apical dendrite of CA2 and CA3a neurons extend into the transverse plane of the hippocampus, while the other CA3 cells preferentially branch in the longitudinal plane [14]. In addition, CA3 neurons project their axons only in the stratum radiatum (SR) of the ipsilateral hippocampus, but axons of CA2 and CA3a neurons target both the apical and the basal dendrites of CA1 neurons, in the SR and in stratum oriens, respectively [15].

Second, the termination zone of afferent projections outlines an area including CA2, as defined by Lorente de Nó, as well as the initial part of CA3a. For example, the fibers coming from the hypothalamic supramammillary nucleus [16] or from the lateral medial septum [17] have a projection pattern that encompasses CA2 and the initial CA3a. While this pattern apparently conflicts with the termination zone of the mossy fibers, it is not clear whether all neurons in the initial part of CA3 are connected by the mossy fibers. The mossy fiber bundle does not end abruptly but becomes finer at its end and it is possible that this region is heterogeneous and composed of a mixed population of mossy fiber-connected CA3 and unconnected CA2 neurons.

Finally, recent studies have found that the CA2 region of the hippocampus is highly enriched in or is the exclusive location of multiple proteins. These proteins include adenosine receptors [18], vasopressin receptors [19], glutamate receptors [20], epidermal growth factor receptors [21], striatal enriched protein tyrosine phosphatase [22], Purkinje cell protein 4 [23], α-actinin-2 [24], and regulator of G-protein signaling 14 [25]. Consistent with other descriptors, the expression pattern of these markers includes the CA2 region and the initial part of CA3a. Thus, based on these different sets of criteria, a more precise definition of CA2 should include the initial part of CA3a.

Furthermore, recent evidence from exhaustive genetic and anatomical studies by the Allen Brain Institute has led to the redefinition of the CA1 and CA2 boundary. By examining the expression profile of non-overlapping protein markers for CA1 and CA2, it was shown that at the

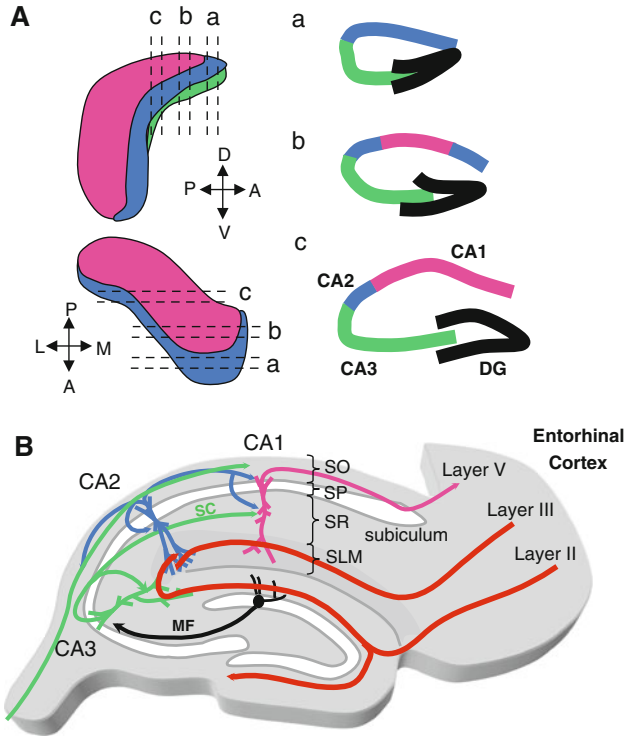

Fig. 1 Anatomy of the hippocampus. **a** (*Left*) Schematic representation of the lateral (*top*) and dorsal (*bottom*) views of the hippocampus. *Dashed lines* indicate the location of three separate sections along the transverse axis shown (*right*). Note that at the most anterior end of the hippocampus (section *a*), only CA2 and CA3 are present, and that in section *b* CA2 is bifurcated by CA1 (adopted from reference [19]). *A* anterior, *P* posterior, *D* dorsal, *V* ventral, *M* median, *L* lateral. **b** Diagram of a transverse section of the hippocampus. The different classes of pyramidal neurons are illustrated with *arrows* indicating the projection pattern of intrahippocampal axonal projections. Glutamatergic inputs from *layer II* and *layer III* of the hippocampus are shown in *red*. *SC* Schaffer collaterals, *MF* mossy fibers, *SO* stratum oriens, *SP* stratum pyramidale, *SR* stratum radiatum, *SLM* stratum lacunosum moleculare

most rostral tip of the hippocampus, CA2 wraps around CA1. Viewed in the coronal plane, CA2 comprises the entire regio superior for about the initial 500 µm of the hippocampus, until it is split in two by the emergence of CA1 [23, 26] (Fig. 1a). These considerations are important, as many studies rely entirely on Lorente de Nó's initial definition of CA2 and fail to include the intial segment of CA3a. As an interesting aside, it is worth mentioning that while CA2 is a relatively small region compared to CA3 or CA1 in rodents, its relative proportion in the hippocampus is much larger in primates, suggesting that it might have an important role in higher cognitive function [11].

Connectivity

Information from the cortex is processed by the hippocampus by several parallel pathways. The main glutamatergic input to the hippocampus comes from the entorhinal cortex, which provides the starting point of the trisynaptic pathway. In this well-studied network, layer II pyramidal neurons in the entorhinal cortex send axons which form synapses with granule cells of the dentate gyrus. These granule cells project axons to CA3 pyramidal neurons through a distinctive thin bundle of fibers referred to as mossy fibers. Mossy fibers target the most proximal part of the apical dendrite of CA3 neurons. CA3 neurons project their axons to the dendrites of CA1 neurons and form synapses in the SR, this well-examined connection is called the Shaffer collateral pathway. The trisynaptic loop is completed by the projection of CA1 axons to the deep layer of the entorhinal cortex, either directly or via the subiculum (Fig. 1b).

In addition to the trisynaptic pathway, the entorhinal cortex also projects to the hippocampus through layer III neurons. Axons of layer III neurons run on the regio superior and directly contact CA1 neurons on the most distal part of their apical dendrite in the stratum lacunosum moleculare (SLM; Fig. 1b). This direct pathway has been much less studied than the trisynaptic pathway, and was initially considered to be a minor input to the hippocampus. The primary reason behind this logic is that it provides a very weak drive to CA1 neurons, and was thus believed to have only a modulatory action on the Shaffer collateral input from CA3 to CA1. However, recent findings have suggested that the importance of this direct input might have been overlooked [27–30]. Its main target might not exclusively be the distal dendrites of CA1 neurons, but the dendrites of the also frequently overlooked CA2 pyramidal neurons [9]. We next describe the morphology of CA1 and CA2 neurons, and illustrate how these two neighboring groups of pyramidal cells, despite both being innervated by axons from cortical and CA3 neurons, differently integrate signals from these two areas.

Dendritic morphology of CA1 and CA2 pyramidal neurons and compartmentalization of synaptic inputs

Dendritic morphology of CA1 and CA2 pyramidal neurons

All pyramidal neurons share typical morphological features in terms of dendritic branching [31]. In addition to having numerous relatively short basal dendrites, pyramidal neurons have a characteristic long apical dendrite that terminates with a dendritic tuft on the most distal end. Proximal to the cell body, numerous oblique dendrites branch directly from the primary apical dendrite, and continue to branch again. For some pyramidal neurons, the main apical dendrite bifurcates into two "sister" apical

branches that can then bifurcate again before giving rise to the most distal dendritic tuft. Usually, the basal dendrites and the proximal region of the apical dendrites contain synapses from local inputs originating from the same area or adjacent areas, while the distal dendritic tuft of the apical dendrite receives afferents from more distant cortical and subcortical areas. Although common to all pyramidal neurons, these characteristics can vary considerably between different layers, cortices and species. The morphological difference between CA1 and CA2 is a prototypical example of this diversity.

CA1 pyramidal neurons have a single apical dendrite that usually does not bifurcate, or bifurcates relatively far from the soma [14]. Numerous secondary oblique dendrites emanate from the apical dendrites in the SR but only a few branches are present in the SLM (Fig. 2). A very different picture emerges for CA2 neurons. Studies in rodents [9, 14, 32] and humans [33] have shown that the apical dendrite of CA2 neurons bifurcates close to the soma into two or three apical dendrites that extend to the SLM. In contrast to CA1, very few secondary oblique dendrites are observed in the SR, but many branches are present in the SLM.

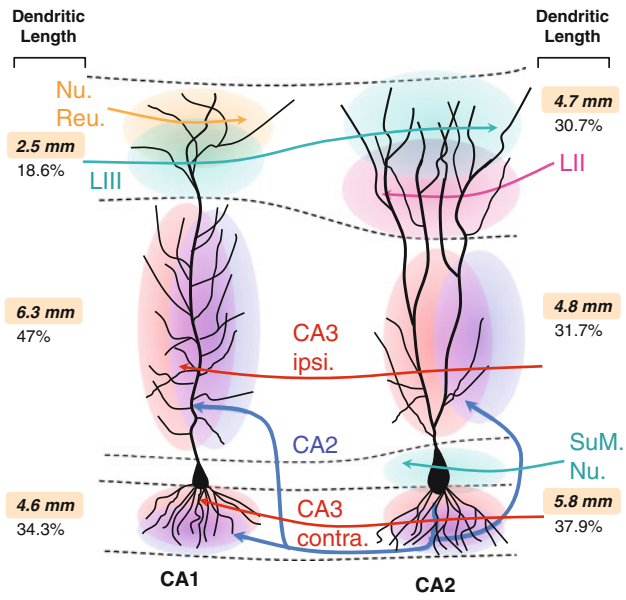

Fig. 2 Dendritic branching and connectivity of CA1 and CA2 pyramidal neurons. The dendritic length in the different hippocampal strata and the percentage of the total dendritic length in each stratum is indicated. Note that the dendrites of CA1 branch most in the SR whereas the dendrites of CA2 branch most in the SLM (adapted from reference [14]). The termination zones of the main inputs to CA1 and CA2 are shown with *colored lines* and *ovals*. While inputs from layer III (*LIII*) of the cortex and from CA3/CA2 are common to both CA1 and CA2 neurons, axonal density from the nucleus reuniens (*Nu. Reu.*) fades out at the border between CA1 and CA2, and layer II (*LII*) fibers and supramammillary nucleus (*SuM. Nu.*) fibers are specific to CA2 neurons

The total dendritic length in the different dendritic compartments has been quantified in rat [14]. The basal dendrites represent around 35% of the total dendritic length in both CA1 and CA2 neurons. However, the length of dendritic branches on the apical dendrite reveals a very different branching pattern between these two classes of pyramidal neurons. While 6.3 mm of dendrites are present in the SR for CA1 neurons (about 47% of total length), CA2 neurons only have 4.8 mm in this compartment (about 31%). Conversely, 4.7 mm of dendrite are present in the SLM for CA2 neurons (about 31%), but only 2.5 mm for CA1 (about 19%) [14].

While the functional implication of the different dendritic morphology is unclear, one may speculate that the predominant branching in different layers (SR for CA1 and SLM for CA2) suggests that these neurons may be preferentially connected by different inputs. In addition, this geometry might strongly influence the firing of the pyramidal neuron. For example, a computational study has shown that even with identical channel distribution, different dendritic morphology was sufficient to change the firing from a continuous to a bursting mode [34]. Furthermore, the geometry of the dendrite will influence the propagation and/or the integration of synaptic potentials [35]. The fact that the apical dendrite of CA2 neurons branches close to the cell body into several large apical dendrites may contribute to the larger EPSPs recorded at the CA2 soma when stimulating distal inputs. Indeed, EPSPs generated on different distal branches can potentially summate proximally where the dendrites converge (see below for more details).

In addition, the forward and back propagation of APs has been shown to be sensitive to dendritic morphology [36]. The back-propagating somatic spikes are necessary for spike timing-dependant plasticity [37]. Therefore, the more proximal bifurcation of the CA2 apical dendrite may lead to a dampening of the spike and thus may restrict the extent of the plasticity evoked along the dendrite. Conversely, this logic would predict an enhanced forward propagation of distally evoked dendritic spikes. A closer examination of these predictions would be informative.

Compartmentalization of excitatory inputs to CA1 and CA2 pyramidal neurons

Consistent with the general trend, proximal dendrites of CA1 and CA2 pyramidal neurons receive local inputs while the more distal dendrites contain synapses with axons originating from the cortex (Fig. 2). CA1 basal dendrites share connections with axons from neighboring CA2 neurons [15] and also with axons that project from contralateral CA3 pyramidal neurons [38, 39]. Ipsilateral CA3 neurons close to CA2 also send projections to the

basal dendrites of CA1 [6, 38, 40], but it is possible that these neurons may be misclassified as CA3 and actually be CA2 (see above). The basal dendrites of CA2 neurons also likely receive input from CA3, but this connection has never been studied and confirmed by electrophysiological recordings. In the SR, Schaffer collaterals from CA3 form synapses onto the proximal region of the apical dendrites of both CA1 and CA2 neurons [6]. CA2 also sends axons to the same region onto CA1 (in addition to targeting the basal dendrite of CA1) [15, 40]. In addition, both basal and apical dendrites of CA2 neurons are likely targeted by ipsilateral CA2 axons [40]. Indeed, the number of recurrent collaterals was initially described to be high in CA2/CA3a [11], but is much less prominent in CA1. Finally, the distal tuft of the apical dendrite of both CA1 and CA2 is connected by cortical inputs. It should be noted, however, that CA1 neurons only receive inputs from layer III of the entorhinal cortex, while both layer III and layer II connect CA2 neurons [7, 8].

Influence of different excitatory inputs onto distinct dendritic domains

Even though CA1 and CA2 share similar inputs on their distal and proximal dendritic compartments, these inputs may be integrated differently because of the different branching patterns in the SLM and SR. This suggests that CA1 and CA2 pyramidal neurons participate in different circuits within the hippocampus. In addition, there are inputs that connect exclusively to CA1 or CA2 neurons, further strengthening this idea (Fig. 2). For example, the thalamic nucleus reuniens projects to the distal dendrites of CA1 but not to those of CA2. This input can also act to modulate the proximal Schaffer collateral inputs, and may provide a convergent signal with cortical inputs onto distal dendrites of CA1. Similarly, CA2 neurons are the only pyramidal cells in the hippocampus that receive fibers from the hypothalamic supramammillary nucleus. The lateral region of this nucleus projects to the dentate gyrus and CA2, while the medial part only targets CA2 neurons [41, 42]. Fibers from this nucleus are glutamatergic but also express different peptides such as substance P or calretinin [43]. One peculiarity of these glutamatergic fibers is that they mostly target the soma of CA2 neurons [44, 45]. This is in contrast to the soma of CA1 pyramidal cells, which is mostly devoid of glutamatergic synapses [4]. Inputs located close to the soma will not be attenuated by cable properties of the dendrites and will thus have a strong impact on AP generation. The precise action of supramammillary inputs is unclear, but in vivo experiments have shown that decreasing activity in the supramammillary nucleus decreases the frequency of the theta oscillation in the hippocampus [46].

Cortical inputs

Both in-vitro and in-vivo studies indicate that cortical inputs have different influences on CA1 and CA2 neurons. The first evidence comes from in vivo studies in the guinea pig, where the different hippocampal areas were recorded during stimulation of the cortical inputs. Experiments performed in Tiziana Gessi's lab demonstrated that during stimulations of increasing intensity of layer II of the entorhinal cortex, responses in CA2 were detected with the lowest stimulation intensity [47, 48]. Increasing stimulation strength evoked a response in CA3 followed by a response in CA1. Pyramidal neurons in CA2 were also the first to generate APs in response to layer II stimulation, and EPSPs were observed in CA1 before APs were generated in CA3. This suggests that CA2 neurons are more responsive than CA3 neurons to layer II stimulation and that CA2 connects CA1 neurons. Similarly, a different study revealed that CA2 neurons are also more responsive to layer III stimulation than CA1 neurons [49]. While the authors only examined the ability to evoke APs in CA1 following stimulation of layer III, they clearly stated that they only observed firing when they recorded at the border CA1/CA2, and not in other parts of CA1. Higher responsiveness of CA2 neurons in response to cortical input stimulation has also been described in mouse hippocampal slices [9]. Several studies have shown that EPSPs recorded in the soma following stimulation of layer III are very small in CA1. Surprisingly, EPSPs recorded in CA2 following the same stimulation were much larger than in CA1 (up to fivefold). In fact, the largest EPSPs recorded extracellularly in the somatic layer in response to stimulation of both layer II and layer III were observed in CA2 neurons. Similar results have been observed with whole-cell recordings of neurons held at −70 mV. This disproves the potential implication of an increased driving force, as CA2 neurons have a more hyperpolarized resting potential than CA1 neurons [9].

While the mechanism(s) responsible for the larger somatic EPSPs in CA2 versus CA1 are currently unknown, several parameters may potentially contribute to this difference (Fig. 3). The attenuation of the EPSPs as they propagate from the tuft to the soma has not been studied in CA2, but is likely to be smaller in CA2 than in CA1. Different studies have estimated that the dendrites of CA1 attenuate distal EPSPs by a factor of 50–100 at the soma [31, 50]. The larger size of the EPSPs recorded at the soma of CA2 neurons indicates that the attenuation in this cell type cannot be as large as in CA1. Indeed, EPSPs of 10 mV are observed in the soma in response to cortical input stimulation. Because the dendritic EPSP amplitude is likely less than 70–80 mV, a limit imposed by the difference between the membrane resting potential and the EPSP

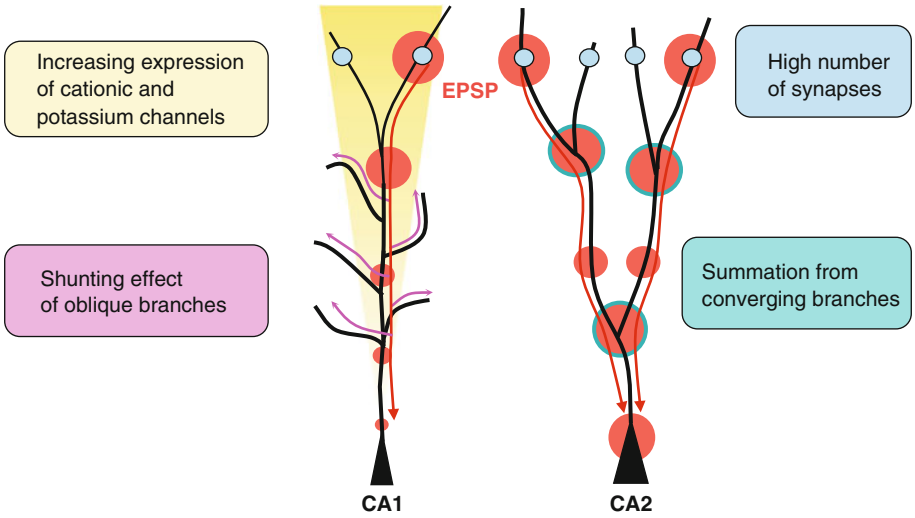

Fig. 3 Potential mechanisms for the large somatic amplitude of distally evoked EPSPs in CA2. In CA1, distal EPSPs display a very large attenuation (50- to 100-fold) as they propagate to the soma. This attenuation in EPSP amplitude and/or propagation results from cable properties of the dendrite including an increasing diameter from distal to proximal, active properties of the dendrite with a proximal to distal gradient of channels such as nonspecific cationic HCN1 channels and the A-type potassium channels, and a loss of current due to the shunting effect of numerous oblique dendrites in the SR. The exact mechanisms underlying the much larger amplitude of distally evoked somatic EPSPs in CA2 is currently not well understood, but may result from a higher number of distal dendritic branches resulting in more potential synapses, different levels and expression patterns of ion channels along the dendritic axis (i.e., reduced distal expression of HCN1 channels), different dendritic geometry with few oblique dendrites in the SR, and summation of EPSPs at points of convergence from dendrites projecting into the SLM

reversal potential (around 0 mV), the resulting attenuation cannot be more than sevenfold to eightfold in CA2, much lower than the 50- to 100-fold attenuation observed in CA1.

Both the dendritic morphology and localization of ion channels contribute to the large decrease in EPSP amplitude from distal dendrites to the soma of CA1 pyramidal neurons. Many oblique dendrites emanate from the apical dendrite of CA1 neurons in the SR. These dendrites exert a shunting effect and greatly contribute to the attenuation of the EPSP amplitude [51]. In addition, the increase in the diameter of the dendrite will also contribute to a decrease in EPSP amplitude as the current propagates from distal to proximal dendrites [51, 52]. Active properties are also known to control EPSP amplitude and propagation. For example, both HCN1 and HCN2 channels (underlying the hyperpolarization-activated nonselective cation current Ih) and A-type potassium channels (Kv4.2) are expressed with an increasing gradient from proximal to distal dendrites of CA1 neurons [52, 53]. These two conductances are known to dampen EPSP amplitude/duration and constrain EPSP/dendritic spike propagation from the tuft to the proximal dendrite [54, 55].

The situation is remarkably different in CA2 neurons in several aspects. The morphology of the dendrite is quite different: the distal dendrites branch much more as they approach the tuft. A CA2 pyramidal neuron has a higher number of dendritic branches in SLM than a CA1 pyramidal neuron. Hence, a single cortical axon is more likely to form a higher number of synapses onto a single CA2 neuron than a single CA1 neuron (see Fig. 3). One potential consequence of such a dendritic geometry is that it permits synaptic signals from different dendrites of the same neuron to summate as the branches merge, thus producing a larger EPSP at the soma. In addition, CA2 neurons have very few oblique dendrites in the SR, minimizing the shunting of current as the EPSP propagates along the dendrite.

Finally, the expression of ion channels in CA2 dendrites is largely unstudied, but might contribute to differences in EPSP propagation between these cell types. It has been shown that expression of HCN subunits is lower in CA2 than in CA1 [56, 57], and electrophysiological recordings indicate a lower density of Ih in CA2 [9]. There have been no electrophysiological studies examining the functional expression of potassium, sodium or calcium currents in the dendrites of CA2 pyramidal neurons. It is possible that the there may be differences in the expression patterns of these channels between CA1 and CA2 dendrites that would lead to a different attenuation of EPSPs. Future studies are required to determine how much the active properties of dendrites in CA1 and CA2 contribute to EPSP propagation.

Schaffer collateral inputs

Unlike what is observed with distal cortical inputs in SLM, experimental evidence suggests that the Schaffer collateral inputs from CA3 evoke larger responses in CA1 than they do in CA2. An initial study performed in acute immature rat brain slices failed to show any difference in EPSP amplitude in CA1 and CA2 neurons following stimulation to CA3 axons [58]. However, EPSPs were subsequently shown to be significantly larger in CA1 than CA2 in adult mice [9]. The lack of difference in immature rats might be a result of the intense remodeling of the branching of CA3 axons that occurs between the juvenile and early adulthood periods of development [59]. In adult mice, larger EPSPs in CA1, as compared to those in CA2, were observed both locally with extracellular recordings as well as at the soma with whole-cell recordings [9]. The larger local synaptic current density in CA1 is consistent with the greater number of oblique dendritic branches in the SR of CA1 neurons and the more extensive branching of CA3 axons in CA1 versus CA2 [38, 60]. This suggests that the larger EPSPs in CA1 following CA3 axon stimulation might result from a greater number of synaptic contacts in CA1.

Synaptic plasticity

The term synaptic plasticity was introduced by the Polish psychologist Konorski in 1948 and describes activity-dependent and lasting changes in the efficacy of synaptic transmission [61]. Hebb further embodied this idea in 1949 in a formal hypothesis known as the Hebbian theory [62], often summarized as "cells that fire together, wire together". Most synapses in the brain express different forms of short-term and long-term synaptic plasticity, including long-term potentiation (LTP), which is believed to be an important phenomenon for learning and memory formation. LTP was first described in the hippocampus by Bliss and Lømo in 1973 [63] and has been extensively studied at the CA3–CA1 Schaeffer collateral synapse. More recently, LTP has been characterized at synapses between CA3 and CA2 [9, 58] at proximal dendrites in the SR, at synapses between cortical inputs and the distal CA1 dendrite in the SLM [64–66] and between cortical inputs and the distal CA2 dendrites in the SLM [9]. As already described for other inputs, these results confirm the general idea that synaptic plasticity is different not only between different inputs, but also between different targets contacted by the same input.

LTP at Schaffer collaterals to CA1 synapses has been studied by many groups and can be evoked with multiple different stimulation protocols, the most common one involving high-frequency stimulation (HFS) trains at 100 Hz. There is general agreement that LTP at this synapse requires postsynaptic calcium influx and results in insertion of new AMPA receptors [67]. However, a presynaptic component has been also described using a theta burst stimulation [68] or a pairing protocol [69, 70]. Regardless of stimulation protocol, this potentiation is usually large (about 50–100%), particularly under conditions where inhibitory transmission is blocked. Similar potentiation is observed at the recurrent collateral CA3–CA3 synapses [71], leading to the idea that the Schaffer collateral axons display a general LTP onto their pyramidal cell targets.

Surprisingly, a study in immature rats using whole-cell recordings of CA2 neurons has shown that the Schaffer collateral inputs onto CA2 are not potentiated following HFS or other protocols classically used to evoke LTP [58]. The lack of LTP has been proposed to result from an efficient calcium extrusion by CA2 neurons [72], and could be rescued by knocking out a protein involved in regulating G-protein signaling [25]. This lack of LTP was confirmed with extracellular recordings in adult mice indicating that it is a general property of these inputs onto CA2 neurons [9].

LTP has also been studied at the direct cortical inputs from layer III to CA1 and CA2 pyramidal neurons in the SLM. Several studies have shown an LTP of low magnitude at the distal cortical–CA1 synapse [65, 66]. The mechanisms underlying this potentiation are not fully understood. It has been found to be blocked by NMDA receptor antagonists, and is increased in HCN1 knockout mice [73]. LTP at this synapse may be due to an increase in glutamate release following recruitment of N-type calcium channels involved in neurotransmitter release [64], suggesting that a retrograde messenger is released by the postsynaptic cell and acts presynaptically to increase release.

Unexpectedly, there is a robust LTP following HFS at cortical inputs at synapses on the distal dendrites of CA2 in the SLM [9]. This is surprising given the dearth of LTP observed in CA2 at Schaffer collateral synapses. While the mechanisms underlying this potentiation are unknown, it is much larger than the one observed in CA1 [9]. Following HFS, layer III inputs onto distal CA2 dendrites display about 60% potentiation, and layer II inputs show about 100% potentiation. This strong LTP may result from the large EPSPs observed at cortical to CA2 neurons. Thus, both basal synaptic transmission and synaptic plasticity appear to be enhanced in CA2 compared to CA1, strengthening the notion that CA2 might be a preferential target of cortical inputs.

Role of inhibition in controlling excitatory synaptic transmission and plasticity

Axons of interneurons also target different compartments of pyramidal neuron dendrites. There are numerous

interneuron subtypes present in the hippocampus [74]. They innervate different domains of pyramidal cell dendrites and fire with distinct temporal patterns during hippocampal oscillations. Thus, with the combination of different firing properties, dendritic arborizations and axonal projections, each interneuron subtype can have a very different impact on AP generation by hippocampal pyramidal neurons [74, 75]. For example, oriens-lacunosum moleculare cells target the apical tuft of pyramidal neurons and are likely to exert specific control of distal excitatory synapses. Conversely, the bistratified cells target basal and proximal apical dendrites and will thus preferentially affect proximal excitatory synapses. Because the strength of these inhibitory synapses are not scaled to compensate for dendritic location, the primary effect of inhibitory synapses might occur locally on the dendrite [76]. Other interneurons, such as basket cells, heavily target the perisomatic region and will thus control firing probability of the pyramidal cell.

In the human hippocampus, the density of interneurons was shown to be the highest in the CA2 area [77, 78]. Similar results were observed when restricting the measure to interneurons expressing parvalbumin [79]. This high density of interneurons in the CA2 region might also apply in rodents, at least for interneurons expressing somatostatin (see reference [80]). In addition, the probability of obtaining a whole-cell recording between a connected interneuron and pyramidal cell is higher in CA2 than in CA1 [81], suggesting a stronger inhibitory drive. Finally, a unique type of interneuron with wide dendritic and axonal projections has been reported in CA2 [81]. The consequences of these peculiar characteristics of interneurons in CA2 are not known, but as described below, they might contribute to the powerful control of EPSP amplitude coming from CA3.

Control of EPSP amplitude

Depending on their main excitatory drive, interneurons belong to two different kinds of networks: feed-forward and feed-back. The feed-forward network consists of interneurons contacting a given pyramidal cell that are activated by the same input that activates the pyramidal cell. Interneurons contacted by the pyramidal cell they synapse onto are part of the feed-back network. Feed-back inhibition does not affect the initial EPSP amplitude onto pyramidal neurons because it is recruited after the firing of the pyramidal neuron. Two types of feed-back inhibition have been described in CA1 [82]. Some interneurons respond quickly to firing of CA1 pyramidal neurons, and stop firing abruptly. These interneurons target the soma and proximal dendrites of CA1 neurons and are called onset-transient interneurons. Other feed-back interneurons require more sustained activation to fire, and are able to maintain their firing. They target the distal dendrites and are called late-persistent interneurons. Conversely, feed-forward inhibition is activated by the same inputs that excite the pyramidal neurons, and thus can have a large effect on EPSP amplitude generated on the pyramidal neuron, even if the inhibitory postsynaptic potential (IPSP) might come with a slight delay after the EPSP. This has been clearly shown in CA1 neurons after stimulating the excitatory inputs from CA3 [83]. The authors were careful not to directly recruit inhibitory fibers that synapse onto CA1 pyramidal neurons by stimulating far from the recorded CA1 neuron. They observed a significant increase in EPSP amplitude from CA3 inputs after blocking inhibitory transmission [83].

The role of inhibition in controlling EPSPs from CA3 input has been compared between CA1 and CA2 neurons. While a significant increase in EPSP amplitude was observed in CA1 after blocking inhibition, the EPSPs were still large with inhibition intact and able to evoke firing during a brief train of EPSPs in a significant number of pyramidal neurons [9]. A very different picture was observed in CA2 neurons. EPSPs were slightly smaller than in CA1 with inhibition blocked. However, with inhibition intact, the EPSPs were completely masked by the IPSPs [9]. In fact, when the EPSP amplitude (recorded without inhibition) was related to IPSP amplitude, a ratio smaller than 1 was observed in CA2, indicating that inhibition prevails over excitation in the proximal dendrite of CA2 neurons (Fig. 4a). This very large feed-forward inhibition in CA2 completely precluded CA3 inputs to drive firing in CA2, even when a train of stimulation was used. However, CA3 inputs were quite efficient in driving firing in CA2 when inhibition was blocked. This suggests that any modulation of inhibition in the CA2 area, particularly a downregulation, might have an important impact on the ability of CA3 to engage CA2. This may be relevant under normal physiological conditions, but also during pathology, as specific decreases in interneuron numbers have been reported in CA2 during schizophrenia [78].

A mirror image is observed when looking at cortical inputs to CA1 and CA2 neurons. Several studies have shown a large feed-forward inhibition in CA1 neurons following stimulation of cortical inputs [84, 85]. Similar to inputs to CA2 from CA3, stimulation of cortical inputs in the SLM recruits strong feed-forward inhibition in CA1. This feed-forward inhibition often completely masks the EPSP. Interestingly, in CA2, the amplitude of the inhibitory component is similar to that seen in CA1 following cortical input stimulation [9]. However, because cortical EPSPs are very large in CA2, the impact of inhibition is minor, and excitation was measured to be fourfold stronger than inhibition (Fig. 3a). These studies show that it is

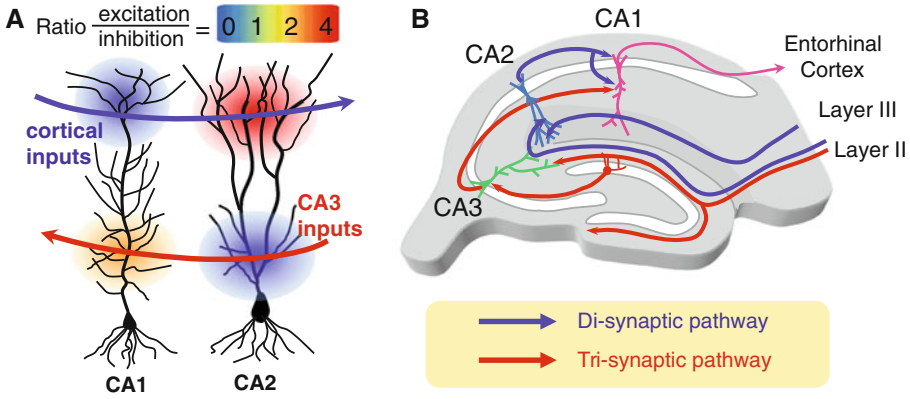

Fig. 4 Driving strength of CA3 and cortical inputs onto CA1 and CA2 neurons: consequences of information flow within the hippocampus. **a** Schematic representation of the net synaptic drive of cortical and CA3 inputs onto CA1 and CA2 pyramidal neurons. Net drive is conveyed as the ratio between excitation and inhibition. Cortical inputs provide a net inhibitory drive to CA1 neurons due to the recruitment of a large feed-forward inhibition while simultaneously providing a strong excitatory drive to CA2 neurons. Conversely, the excitatory signal from CA3 is dominated by a strong feed-forward inhibition at CA2 but provides a net excitatory drive to CA1. **b** Schematic illustration of the transfer of information within the hippocampus. The classic trisynaptic pathway is engaged by layer II neurons of the entorhinal cortex and involves successively the dentate gyrus, and CA3 and CA1 pyramidal neurons. In the disynaptic pathway, axons of both layer II and layer III neurons converge onto the dendrites of CA2 neurons, which in turn send axons to CA1. While these pathways can function independently, there may be instances when the inhibitory gate between CA3 and CA2 is reduced, allowing an interaction between the di-synaptic and tri-synaptic pathways.

essential to know both the magnitude of EPSP amplitude as well as how much inhibition is recruited by excitatory inputs at different locations, and how this inhibition affects the net EPSP amplitude. Otherwise, it is difficult to determine the likelihood of a presynaptic group of neurons engaging a postsynaptic target.

Control of synaptic plasticity at excitatory synapses

GABAergic synapses not only control the amplitude of the EPSP, but also the ability of excitatory synapses to express plasticity. Modulating the strength of inhibitory synapses is thereby a powerful means to control plasticity at excitatory synapses. The first evidence for this came from a study of LTP at Schaffer collateral to CA1 synapses, which was shown to be highly dependent on the level of inhibition [86]. In fact, when inhibition was intact, little LTP was evoked by HFS. However, pharmacological block of GABA receptors allowed the same stimulation to evoke a much larger potentiation. A similar restriction of LTP by inhibition was also observed at cortical-CA1 synapses [65]. While all GABA-A receptors were pharmacologically blocked in these studies, there is evidence that a more subtle and local change in inhibition is also efficient in controlling LTP at excitatory synapses. GABAergic terminals express several receptors that can control the release of GABA. For example, interneurons expressing the peptide CCK also express cannabinoid CB1 receptors at their terminals. Activation of these receptors by endocannabinoids powerfully decreases the release of GABA. Endocannabinoids are retrograde messengers released by the postsynaptic cell that mediate both short- and long-lasting depression of transmitter release at many synapses throughout the brain [87]. In the CA1 region of the hippocampus, both short-term [88] and long-term [89] depression of GABA release by endocannabinoids has been described. Although different protocols were used to trigger the release of endocannabinoids during short- and long-term plasticity, in both cases the release was very localized. During short-term plasticity, cannabinoid release occurs throughout a single pyramidal cell; during long-term plasticity, it occurs on many pyramidal cells but is restricted to a portion of the dendrite. Both short-term [90] and long-lasting [91] depression of GABAergic transmission have been shown to facilitate LTP induction at excitatory synapses. Whether or not a short- or long-lasting depression of GABAergic synapses exists in CA2 is not yet known. However, given the high level of inhibition in CA2 and its strong impact on the amplitude of the EPSPs from the Schaffer collaterals, any activity-dependent change in GABAergic transmission, particularly a decrease, is likely to have a profound effect on the ability of CA3 inputs to engage CA2 neurons, and thus, to open the gate between CA3 and CA2.

Consequences of information flow within the hippocampal network

In contrast to Schaffer collateral inputs to CA1, cortical inputs are very weak and usually unable to evoke AP output in CA1 neurons. The role of cortical inputs might

therefore be to modulate the Schaffer collateral inputs rather than serve as a primary drive to CA1 neurons. Indeed, cortical input EPSPs are usually unable to evoke a dendritic spike that propagates to the soma. However, when paired with Schaffer collateral stimulation, activation of cortical inputs could highly facilitate the generation and propagation of dendritic APs [92]. In addition, several studies have shown the ability of cortical inputs to modulate plasticity at the Schaffer collateral synapses. Given these results, this effect is likely complex because both a facilitatory and an inhibitory effect on LTP at the Schaffer collaterals have been described [93–96].

The driving force of the same cortical inputs is quite different in CA2 neurons, where they have been shown to be able to evoke AP output [9]. In fact, EPSPs evoked by distal cortical inputs were as large as those evoked by the proximal Schaffer collaterals when inhibition was blocked. The importance of cortical inputs to CA2 was even more pronounced when inhibition was intact. While inhibition only had a mild effect on the EPSPs evoked by cortical inputs, it completely nullified the EPSPs evoked by the Schaffer collaterals and prevented this input to drive CA2 [9]. This reversed synaptic drive along the dendrites of CA1 and CA2 undoubtedly has important consequences for the flow of information within the hippocampal network. While the primary drive for CA1 neurons originates from the hippocampus, i.e. CA3 and CA2 inputs, CA2 is strongly engaged by extrahippocampal input from the cortex. This suggests that in addition to the classical trisynaptic loop connecting successively layer II of the cortex, the dentate gyrus, CA3 pyramidal neurons and then CA1 pyramidal neurons, there is an additional and shorter loop, i.e. a disynaptic pathway linking layer II and layer III to CA1 via CA2 neurons (Fig. 4b).

Additional evidence for an alternative hippocampal circuit was reported by Sekino et al. [97]. By using voltage-sensitive dyes and performing optical recordings of membrane potential changes, it was reported that information transfer followed two modes of propagation through the hippocampus after stimulation of dentate gyrus mossy fibers. There was fast propagation of membrane potential changes from the dentate gyrus to CA3 to CA1, likely following the trisynaptic pathway without any activation of CA2. There was also slow propagation which resulted in the recruitment of CA2 neurons [97]. The authors' interpretation of the slow propagation involved a quadrisynaptic pathway (dentate–CA3–CA2–CA1). However, this slow propagation was observed only during strong stimulation, and a large optical signal was also apparent in the SLM of CA3. Given that mossy fibers make synapses in the very proximal part of the apical dendrite of CA3 neurons, i.e. far from the SLM, it is possible that the CA2 neurons were activated by the inadvertent stimulation of cortical inputs running in the SLM of CA3, and not the CA3 neurons themselves. This would be consistent with the disynaptic loop observed by electrophysiological recordings in vivo and in slice recordings, and also with the lack of activation of CA2 by stimulation of mossy fibers and CA3 neurons (due to the large feed-forward inhibition from CA3 to CA2). It is possible, however, that a quadrisynaptic pathway may emerge under conditions in which inhibition is reduced sufficiently to allow CA3 neurons to drive CA2 neurons.

In vivo studies have provided the first evidence for the disynaptic loop [47, 48]. However, because the CA2 area has been overlooked for decades, most interpretations of the transfer of information have been based on the trisynaptic pathway. Nonetheless, recent evidence suggests that a single trisynaptic loop is not sufficient to explain some peculiar results of information flow through the hippocampus. For example, the use of a genetic approach to block synaptic transmission between CA3 and CA1 quite surprisingly had very little effect on hippocampal-dependent memory formation or on CA1 firing in vivo [27]. The interpretation of this result was that the layer III cortical inputs that connect directly to CA1 distal dendrites are sufficient to maintain a coherent firing in CA1 and enable memory formation. However, given the weak ability of cortical inputs to drive firing of CA1, this interpretation may not be very sound. With results from in vivo studies and slice recordings in CA2 suggesting the presence of an additional disynaptic loop [9, 47, 48], a different and perhaps more satisfying explanation emerges. Rather than a monosynaptic loop with layer III directly driving CA1 via distal dendritic synapses, layer III might drive CA1 through a disynaptic loop via CA2. However, in mice lacking CA3 output the consolidation of previously acquired memory and the frequency of ripples (high frequency oscillations) or the ripple-associated reactivation of experience-dependent firing patterns of CA1 neurons are affected, suggesting a role of the trisynaptic pathways in these processes [98]. Future studies with genetic lesions of CA2 neurons or of their synaptic transmission will help elucidate the precise role of the disynaptic loop in hippocampal function.

An interesting peculiarity of CA2 neurons is that they are the only pyramidal neurons in the hippocampus to receive afferents known to participate in controlling the theta oscillation, an important rhythm for hippocampal function. This is the case for the supramammillary nucleus, a hypothalamic structure that controls the frequency of the theta oscillation. The lateral part of this nucleus contacts both CA2 and the dentate gyrus, while the median part specifically targets CA2 through substance P-containing fibers [41, 42]. In vivo experiments have shown that decreasing activity of the supramammillary nucleus also decreases the frequency of the theta rhythm in the

hippocampus [46]. The frequency change is small, but some studies have indicated that minor changes in theta frequency can have an important impact on learning ability, and a strong correlation between theta frequency and learning capacity has been reported in rats [41]. The CA2 area has been suggested to be an intrinsic oscillator in cultured hippocampal slices [99]. Furthermore, CA2 neurons show many recurrent collaterals, and they send their axons not only to CA1, but also to CA3. Thus, this area is ideally located to enable the synchronization of different hippocampal regions. In addition, CA2 neurons appear to be electrically coupled by gap junctions (at least in slice culture), and this coupling is highly enhanced by the muscarinic receptor agonist charbacol [99], which is commonly used to evoke theta oscillations in slice preparations. Further evidence that an intrinsic oscillatory activity is present in CA2 comes from a study performed in human epileptic hippocampus. The epileptic bursts recorded throughout the hippocampus were generated in the CA2 area [33]. In the guinea pig, burst discharges in disinhibited hippocampal slices have also been reported to be generated in the CA2 area [100]. While epileptic activities are different from physiological oscillations, they both result from a synchronization of the network and might share several properties.

Conclusion

There is mounting evidence that CA2 may play a significant role in the overall function of the hippocampus. For example, a recent examination of vasopressin receptor V1b knockout mice has shown a deficit in episodic memory of temporal order [101]. The V1b receptor is highly expressed in CA2, but is not detectable in other parts of the hippocampus [19]. In addition, lesions at the border CA3/CA2 have been found to impair hippocampal operant conditioning [102]. In order to understand how CA2 is contributing to overall hippocampal function, it is becoming evident that the hippocampal circuit may need to be re-examined.

Traditionally, the corticohippocampal network has been considered as a simple network. Most interpretations of physiological, behavioral or computational studies are based on the trisynaptic loop as the main pathway for the transfer of information through the hippocampus. Recent experiments have challenged this paradigm, revealing the presence of parallel and independent routes for information flow within the network. A disynaptic loop is also present between the cortex and the hippocampus, as CA2 receives strong input from both layer II and layer III of the cortex. Furthermore, there may be a quadrisynaptic pathway which is controlled by feed-forward inhibition between CA3 and CA2.

Future directions

It is clear that CA1 and CA2 pyramidal neurons have very distinctive dendritic properties. The different dendritic morphology and dendritic integration allows these two neighboring groups of pyramidal cells to discriminate different sets of synaptic input, and enables them to direct the flow of information within the corticohippocampal network in a specific way. These two classes of neighboring pyramidal neurons are an ideal system for testing many of the proposed models for passive and active dendritic integration. Furthermore, a closer investigation of the different populations of receptors and ion channels as well as their different expression patterns along the dendritic axis of these two populations of neurons could be very constructive for understanding dendritic information processing.

In order to better grasp the implications of the parallel pathways of information flow in the hippocampus, and to put CA2 into a larger context of overall hippocampal function, an elucidation of the axonal outputs of CA2 is required. For example, the fact that CA2 neurons send axon collaterals to CA3 challenges the concept of linear and unidirectional transfer of information in the hippocampus, and a reexamination of current dogma is demanded. Furthermore, CA2 axons target regions outside the hippocampus, and potentially serve as an important output of the hippocampus in addition to CA1. Axon collaterals of CA2 have been shown to project to the septum [15], and it is possible that bidirectional connections between CA2 and the septum are present. Intriguingly, bidirectional connections may also exist between CA2 and the cortex, supramammillary nucleus or other structures. Thus, it is likely that information processing by the hippocampus is achieved by multiple loops working either independently or in parallel.

Fortunately, with the advent of powerful genetic tools and novel methods for precisely tracing synaptic connections, the individual contributions of each region, and eventually each set of synaptic inputs and outputs in the hippocampal circuit can be investigated.

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