CHAPTER

8

Microcircuits of the Hippocampus

The hippocampus is a cortical structure with a simpler and more orderly organization than the neocortex. Over the last decades, the rodent hippocampus has been one of the most frequently used model systems to study the structure, dynamics, and function of mammalian cortical circuits. Entire subfields of neuroscience rest on discoveries made in the rodent hippocampus, particularly the fields of learning and memory, synaptic plasticity, and spatial navigation. The hippocampus is an ideal model system for basic science studies because of its simple circuit organization. Also, from a translational viewpoint, the hippocampus deserves our attention given its role in Alzheimer's disease and many forms of epilepsy. In this chapter we will first introduce the overall circuit layout of the hippocampus, then we will review its main subdivisions, and finally we will discuss specific local circuits.

CIRCUIT LAYOUT OF THE HIPPOCAMPUS

The human hippocampus (together with the fornix, a C-shaped fiber) resembles a seahorse, which is the origin of the name, which is Greek for horse sea-monster. In the rodent, the hippocampus is a banana-shaped brain structure (Fig. 8.1). Most hippocampal studies use

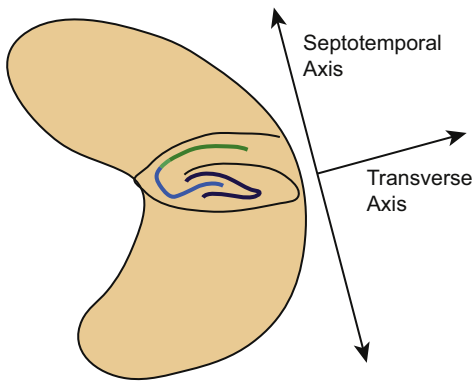

FIGURE 8.1 Schematic representation of the rodent hippocampus. Slice electrophysiology studies typically use transverse sections, which are orthogonal to the septotemporal axis.

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slices that are in the *transverse* plane, orthogonal to the *septotemporal axis* that connects the two endpoints of the figurative banana. Technically, the term *hippocampus* is reserved for part of the so-called *hippocampal formation*, and is composed of the *CA1*, *CA2*, and *CA3 subfields*. CA stands for the Latin *cornu ammonis*, or horn of the ancient god Amun. The hippocampal formation also includes the *dentate gyrus*, *subiculum*, *presubiculum*, *parasubiculum*, and the *entorhinal cortex*. Here we will follow the more common use of the term hippocampus to denote the entire hippocampal formation (Fig. 8.2).

Classically, the hippocampus is a *trisynaptic* (ie, three-synapse) circuit (Fig. 8.3). Information comes in through the superficial layers of the entorhinal cortex. Cells in layer II of the entorhinal cortex project to the dentate gyrus and CA3 of the hippocampus. This pathway is called the *perforant path*, since the axons perforate the subiculum, which is located between

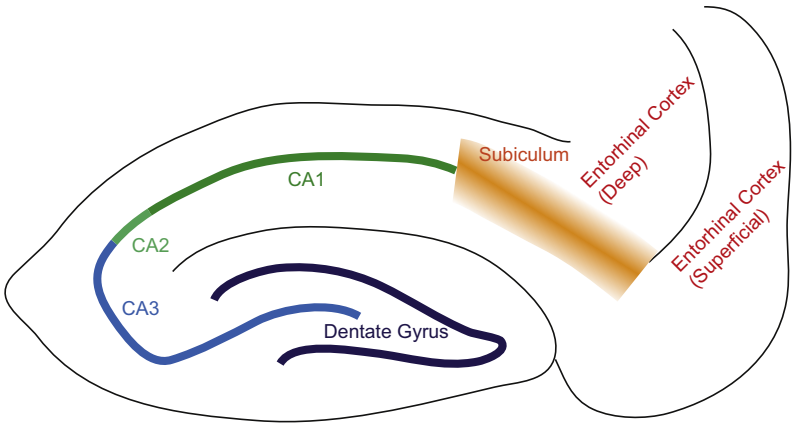

FIGURE 8.2 Overview anatomy of the hippocampal formation in the rodent. The dentate gyrus (dark blue), CA3 (light blue), CA2 (light green), and CA1 (dark green) all exhibit a very thin, densely packed layer of cell bodies (indicated by *thick lines*). In contrast, cells in the subiculum are more spread out. The entorhinal cortex (red) is separated into superficial and deep layers.

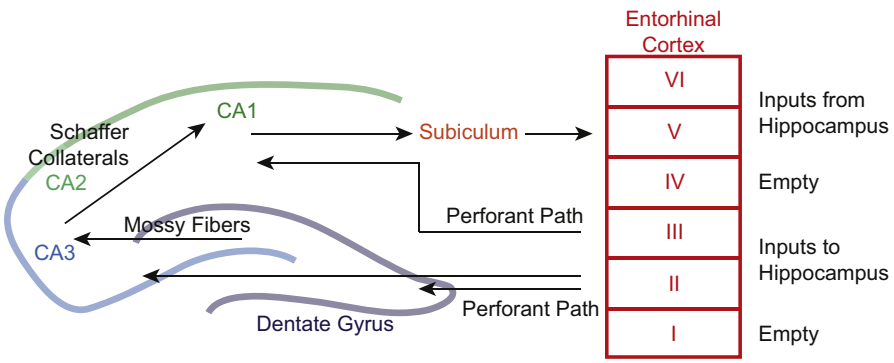

FIGURE 8.3 (Left) Transverse hippocampal section with the main pathways drawn as labeled arrows. (Right) Symbolic representation of entorhinal cortex with its layers I–VI.

the entorhinal cortex and the dentate gyrus. Cells in the dentate gyrus project to CA3 pyramidal cells; the projecting axons form the *mossy fibers*. Pyramidal cells in CA3 form both recurrent connections onto other pyramidal cells in CA3 and project to CA1. This pathway is called the *Schaffer collaterals*. Pyramidal cells in CA1 project to the subiculum and to deep layers of the entorhinal cortex (as does the subiculum).

The dentate gyrus engulfs the CA3 region. The part of the granule cell layer located between CA3 and CA1 is called the *suprapyramidal* layer; the other part is called the *infrapyramidal* layer. The hippocampus itself is divided into subfields CA1, CA2, and CA3. CA2 is a small but distinct subfield in between CA1 and CA3. The subiculum, presubiculum, and parasubiculum are subsumed by the term *subicular complex*. The subiculum starts where CA1 ends (which is defined by the furthest point to which Schaffer collaterals reach) and (in rodents) the dense pyramidal cell layers start to widen. Three major fiber bundles are part of the hippocampal formation. First, the *angular bundle* connects the hippocampus to the entorhinal cortex. Second, the *fimbria–fornix pathway* connects the hippocampus to the basal forebrain, hypothalamus, and brainstem. Third, the hippocampi of the two hemispheres are connected by the *dorsal* and *ventral commissures*. Next, we will discuss the dentate gyrus, hippocampal fields CA1 and CA3, the subiculum, and the entorhinal cortex.

DENTATE GYRUS

The dentate gyrus is a three-layered structure. From the outside there is a relatively cell-free layer called the *molecular layer*, followed by the *principal cell* (or *granule cell*) *layer*, which is densely packed with *granule cells*, and most deeply there is the *polymorphic cell layer*. Granule cells are small cells with elliptical somata that send their dendritic tree into the molecular layer. Granule cells are one of the few cell types in the CNS that undergo adult neurogenesis—new neurons are formed even in adulthood. The axons of the granule cells connect to hippocampal CA3 neurons. Just underneath the granule cell layer are a large number of different types of interneurons. Both the molecular layer (albeit sparsely) and the polymorphic cell layer are occupied by multiple classes of (poorly characterized) neuron types. The dentate gyrus receives its input from the entorhinal cortex (predominantly from layer II); these axons synapse onto the dendrites of the granule cells in the molecular layer. The dentate gyrus in turn projects to CA3 and CA2. The axons from the granule cells are called *mossy fibers* and terminate in CA3 and CA2. Mossy fibers form unique connections with the dendrites of CA3 pyramidal neurons in the form of *en passant* presynaptic terminals called *mossy fiber expansion*s, which are a particularly large presynaptic zone with postsynaptic specializations, *complex spines*, on CA3 neurons.

HIPPOCAMPAL FIELDS: CA1, CA2, AND CA3

In the hippocampus itself, the main cell layer is the pyramidal cell layer (Fig. 8.4). This layer is most densely packed in CA1, and is less densely packed in CA2 and CA3.

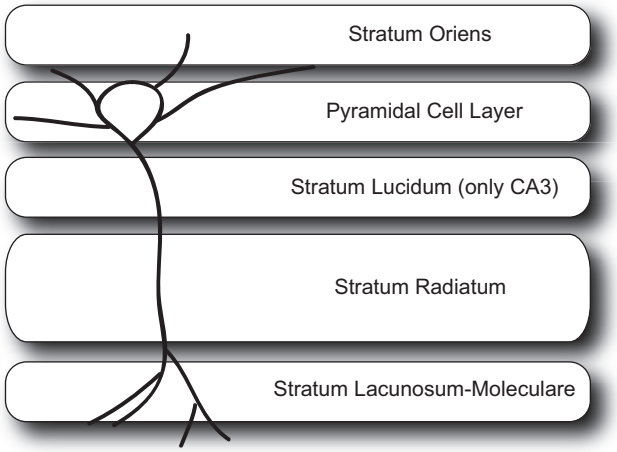

FIGURE 8.4 Layers of the hippocampus shown relative to the position of a pyramidal cell. Note that in contrast to the neocortex, the circuitry for the hippocampus is drawn in a way that the apical dendrites point down, not up.

Above the pyramidal cell layer is the *stratum oriens*, home to the basal dendrites of pyramidal cells and multiple types of interneurons, and is the primary site of input from CA2 neurons. In CA3 and CA2, there is a thin layer just adjacent to the pyramidal cell layer in which the mossy fibers from the dentate gyrus are located, the *stratum lucidum*. Below the pyramidal cell layer (and the stratum lucidum in CA3) is the *stratum radiatum*, in which the recurrent (association) connections within CA3 and the connection to CA1 (Schaffer collaterals) are located. Below the stratum radiatum is the *stratum lacunosum-moleculare*, the recipient zone of input from the entorhinal cortex. Both the stratum radiatum and the stratum lacunosum-moleculare are home to diverse types of interneurons. Pyramidal cells in CA3 are quite variable in their size, while pyramidal cells in CA1 are smaller than the ones in CA3 and are uniform in size. We will focus our discussion on CA1 and CA3 pyramidal cells, which are best understood. Also, to avoid repetition of the previous chapter "Microcircuits of the Neocortex," we will not catalog the different inhibitory interneurons. Instead, we discuss several functional roles of synaptic inhibition in the last section of this chapter.

CA1 Pyramidal Cells

CA1 pyramidal neurons (Fig. 8.5) are among the best-studied neurons in the mammalian nervous system. In the rodent preparation, these neurons are easily accessible for both intracellular and extracellular recordings (in acute slices and intact animals, respectively) and have an afferent pathway, the Schaffer collaterals, that is straightforward to activate and interpret. A further advantage is that it is feasible to record from large apical dendrites using dendritic patch clamp recordings. The dendrites of CA1 pyramidal cells are organized into the *apical* and *basal* dendrites. The basal dendrites are located in the stratum oriens and the apical dendrites are situated in the stratum radiatum (proximal, ie, close, to the cell body) and the stratum lacunosum-moleculare (distal, further away from the cell body).

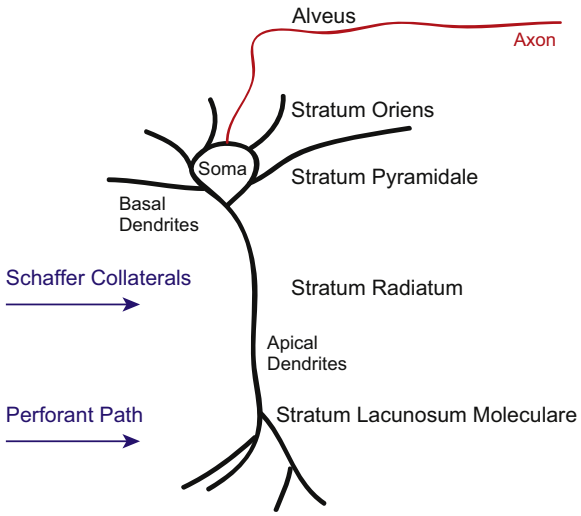

FIGURE 8.5 CA1 pyramidal cell. Blue: Afferent inputs. Red: Axon.

Each CA1 pyramidal cell exhibits around 30,000 spines that receive excitatory input. Direct input from layer III of the entorhinal cortex (perforant path) targets the distal apical dendrites in the stratum lacunosum-moleculare. In contrast, input from CA3 (Schaffer collaterals) forms synapses on the apical dendrites in the stratum radiatum and on the basal dendrites in the striatum oriens. The stratum oriens is the main target of projections from CA2. Also CA1 pyramidal cells are targeted by a diverse set of inhibitory interneurons. For example, the oriens-alveus/lacunosum-moleculare interneurons project to the stratum lacunosum-moleculare and target the apical dendritic branches also targeted by the projections from the entorhinal cortex. The axons of CA1 pyramidal cells project through the striatum oriens in the alveus. In contrast to CA3, almost no collaterals to other CA1 pyramidal neurons are formed.

The most important targets of CA1 pyramidal cell axons within the hippocampus are the pyramidal cells in the subiculum. CA1 pyramidal cells also project to brain areas beyond the hippocampus such as the medial frontal cortex and the olfactory bulb.

The relatively large and complex morphology of CA1 pyramidal cells creates unique challenges for signal propagation [1]. In particular, given the long and elaborate structure of the dendritic tree, distal synaptic input may fail to reach the soma. At least two mechanisms to counteract loss by signal attenuation have been identified. First, the synaptic conductances in the stratum radiatum scale with distance from the cell body such that more distant synapses generate higher-amplitude synaptic currents to compensate for the signal loss caused by propagation to the soma. This mechanism is referred to as *synaptic scaling*. However, synaptic scaling does not apply to the more distal input in the stratum lacunosum-moleculare. Instead, input into the distal dendrites is amplified by voltage-gated ion channels in the dendrites. Simultaneous patch-clamp recordings of dendrites and the soma (see chapter: Membrane Voltage) have shown that injecting current at different distances from the soma always elicited the same response at the soma [2].

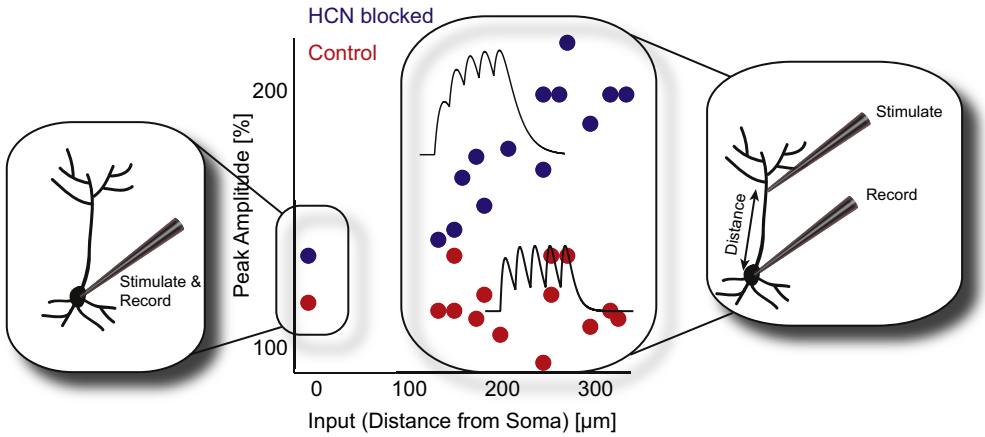

FIGURE 8.6 I_h (mediated by hyperpolarization-activated, cyclic nucleotide-gated, HCN, channels) compensates for spatial filtering by the dendritic tree and enables location-independent synaptic signaling. With HCN channels, the response to stimulation is independent from distance to the soma (control condition, red). Without HCN channels, the amplitude increased with distance because of the temporal smearing of the input, which caused temporal summation of the responses (blue). *Adapted from Magee JC. Dendritic I_h normalizes temporal summation in hippocampal CA1 neurons. Nat Neurosci 1999;2(9):848.*

This finding is in conflict with the cable equation that predicts more temporal smoothing of more distal input. Blocking the hyperpolarization-active depolarizing current (I_h) unmasked such a spatial dependence of the response to the input as a function of distance (Fig. 8.6). I_h deactivates in response to depolarizing (synaptic) input, and therefore it helps shorten excitatory input. In contrast, the amplitude of the incoming excitatory postsynaptic potential (EPSP) is less affected by the relatively slow deactivation time constant of hyperpolarization-activated, cyclic nucleotide-gated (HCN) channels that mediate I_h. There is a strong gradient in the density of HCN channels along the dendritic tree. In agreement with this proposed role of shortening the time course of excitatory events that arrive at distal sites of the dendritic tree, channel density is the highest at the distal end of the dendritic tree.

Voltage-gated ion channels in the dendrite also play a role in the propagation of action potentials from the soma into the dendrites. Specifically, action potentials originate in the initial axonal segment and then backpropagate into the soma and the dendritic tree. This backpropagation is mediated by voltage-gated sodium channels that are uniformly distributed along the somatodendritic axis. Calcium channels are also present in the dendrites, again with approximately constant density. These voltage-gated channels, which enable backpropagating and dendritic action potentials (see toolbox: Neurons), are kept in check by potassium channels in the dendrites. In particular, there is a spatial gradient for the A-type potassium channel that increases nearly linearly with distance on the primary apical dendrite away from the soma [3]. A-type potassium channels exhibit rapid activation and inactivation kinetics. This increase in A-type potassium channels leads to a rapid decrease of the amplitude of the backpropagating action potential. Another important role of backpropagating action potentials is to provide postsynaptic depolarization for long-term

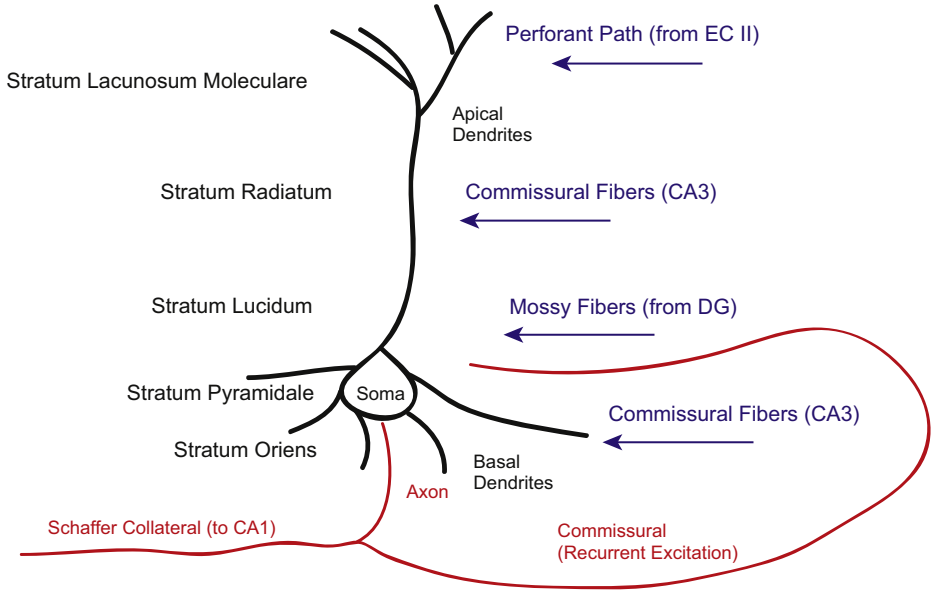

FIGURE 8.7 Pyramidal cell in CA3. *CA*, Cornu ammonis; *DG*, Dentate gyrus; *EC II*, entorhinal cortex layer II.

potentiation. Both backpropagating action potentials (more proximal to the soma) and locally (ie, dendritically) generated action potentials can play this role (see also chapter: Synaptic Plasticity).

CA3 Pyramidal Cells

Pyramidal cells in CA3 (Fig. 8.7) are similar in overall morphology to CA1 pyramidal cells. But in contrast to CA1, CA3 is a highly excitable, recurrently connected network by means of the prominent lateral axon collaterals within CA3. Pyramidal cells in CA3 receive three main classes of excitatory input. First, CA3 pyramidal cells receive input from the entorhinal cortex (layer II) via the perforant path that targets the distal apical dendrites in the stratum lacunosum-moleculare. Second, the input from dentate granule cells is localized to the most proximal part of the apical dendrite (in the stratum lucidum). Third, commissural input is provided by axonal collaterals of other CA3 pyramidal cells that form synapses both in the stratum radiatum and in the stratum oriens. CA3 pyramidal cells connect to CA3, CA2, and CA1 and also the lateral septal nucleus. Unlike CA1 pyramidal cells, CA3 neurons are more prone to intrinsic bursting (firing of several action potentials in an all-or-none fashion). Interestingly, under pathological conditions (experimentally mimicked by suppression of synaptic inhibition or reduction of potassium currents), there are network-wide bursts in CA3. These bursts are referred to as *paroxysmal depolarization shifts*. They are a network phenomenon, since they are mostly mediated by giant excitatory postsynaptic potential, which results from the synchronous activity of large groups of pyramidal cells [4]. This contrasts to physiological bursts in CA3 that are intrinsically generated by voltage-gated ion channels and do not require synaptic transmission to occur.

SUBICULUM

The subiculum represents the major output from the hippocampus. In turn, the subiculum receives input from the superficial layers of the entorhinal cortex and CA1. Therefore subicular neurons (mostly pyramidal cells) receive synaptic input from axons from both areas, with the projections from entorhinal cortex being limited to the more distal dendrites. The subiculum also receives input from many of the brain structures that project to the entorhinal cortex. Pyramidal cells in the subiculum form both local collaterals (targeting other pyramidal cells within the subiculum) and projecting collaterals that target layer V of the entorhinal cortex and also the pre- and parasubiculum. The subiculum also projects to many other brain areas, including the medial prefrontal cortex and many other (sub-) cortical structures. In terms of their electrophysiology, the most prominent features of pyramidal cells in the subiculum are their propensity to fire bursts of action potentials (mediated by a Ca-dependent after-depolarization) and their *subthreshold oscillations*. These oscillations are periodic, small-amplitude fluctuations of the membrane voltage that arise from the dynamic interaction of voltage-gated ion channels that are activated for subthreshold membrane voltages.

ENTORHINAL CORTEX

The entorhinal cortex is the gateway to and from the hippocampus. In essence there are four layers that contain cells (called layers II, III, V, VI according to Cajal; labels are designed to match the neocortex as much as possible) and two layers without cells (I and IV, the latter termed *lamina dissecans*). The superficial, cell-containing layers include *stellate cells* and smaller pyramidal cells. The deep layers contain pyramidal cells (layer V) and cells with a variety of morphologies (layer VI). Stellate cells in layer II have a star-like appearance, with dendrites radiating out from the soma toward both layer I and layer III. Their axons target both granule cells in the dentate gyrus and CA3. Layer II stellate cells exhibit subthreshold oscillations in response to depolarizing current injections in vitro. The frequency of this oscillation ranges from 5 to 15 Hz and corresponds to the theta frequency band as defined in rodents (since there are no thalamocortical alpha rhythms, the theta frequency range is expanded, see chapter: Theta Oscillations). These oscillations are mediated by an interplay of the hyperpolarization-activated depolarizing current I_h and the persistent sodium current I_{NaP}. The pyramidal cells in layer II do not exhibit such subthreshold dynamics, but their projections to the dentate gyrus and CA3 are similar to stellate cells..

The deep layers of entorhinal cortex contain both pyramidal cells and polymorphic neurons (heterogeneous group of neurons). These neurons project to other cortical areas, many of which in turn project to the superficial layers of the entorhinal cortex. In addition, axon collaterals from these neurons also target other cells within the deep layers and the superficial layers. These projections close the loop formed by the superficial layers to the hippocampus and the hippocampal projections back to the deep layers of the entorhinal cortex. Similar to stellate cells in layer II, pyramidal cells in the deep layers exhibit subthreshold oscillations in

the theta band. However, these cells exhibit no I_h and so the mechanism for the genesis of subthreshold oscillations may differ between the two cell types. In the presence of activated muscarinic acetylcholine receptors, layer V pyramidal cells exhibit persistent activity after a depolarizing current pulse. Such sustained activity in the absence of input has been speculatively linked to the role of the entorhinal cortex in memory.

FUNDAMENTAL LOCAL CIRCUIT PRINCIPLES

We will now turn our attention to the fundamental principles of synaptic interaction in the hippocampal circuit. Many of the concepts discussed here in the context of the hippocampus also apply to the neocortex (see chapter: Microcircuits of the Neocortex).

The first principle focuses on the number and classification of cell types in the hippocampus. Overall, there are two types of cells: principal cells and interneurons. Strikingly, interneurons constitute only a small fraction of all hippocampal neurons and defy any simple classification approach. For example, although interneurons are classically thought of as inhibitory, this assumption is likely not true in all cases. Cells that release GABA (chapter: Synaptic Transmission) do not necessarily inhibit their postsynaptic target (eg, during development). Furthermore, inhibitory interneurons may not contribute to an overall reduction in activity levels in the circuit since they inhibit other inhibitory interneurons. Also their definition as local interneurons may be inappropriate since there are interneurons that connect to targets outside of the hippocampus. Efforts to classify interneurons are ongoing and are briefly discussed in the chapter "Microcircuits of the Neocortex."

The second principle concerns the stereotyped arrangement of local synaptic connectivity in the circuit. There are several common connectivity patterns, also referred to as *circuit motifs*, that are ubiquitously present (to different extents) across the brain. We briefly mentioned them in the chapter "Microcircuits of the Neocortex," but will review them in detail here since the hippocampus (in particular its acute slice preparation) has been at the center of elucidating the dynamics of these motifs. We will discuss one excitatory connectivity motif (recurrent excitation) and three inhibitory motifs (feedforward inhibition, feedback inhibition, and mutual inhibition).

Excitatory Circuit Motifs

Pyramidal cells in subfield CA3 exhibit much more pronounced lateral (ie, recurrent) connections than the ones in CA1. The majority of excitatory inputs to CA2 and CA3 pyramidal cells stem from their recurrent collateral axons. CA3 pyramidal cells have large axonal arbors. In CA3, the recurrent synapses create EPSPs of around 1−2 mV, and are therefore far from being able to trigger postsynaptic action potentials. However, the effect of a burst of action potentials is quite pronounced because of augmentation of the synaptic response. In contrast, recurrent connectivity of pyramidal cells in CA1 is more limited and the axonal arbors are much smaller in size. This difference in recurrent excitation makes not only the computational properties of the circuits but also their susceptibility to pathological activity patterns (eg, epileptic seizures) very different. Circuits with sufficient recurrent excitation have the

important computational property of an *attractor network*. These networks have unique properties that enable the occurrence of distinct activity patterns (multistability) that have been associated with different items stored in memory. Any of these patterns can be activated by a partial input since the recurrent connections amplify and thereby complete the initial activation pattern. Furthermore, the recurrent excitation helps to maintain firing patterns even after withdrawal of the initial input and therefore potentially enables short-term memory capabilities. In terms of pathological activity, the difference in the presence of recurrent excitation leads to differential susceptibility of CA3 and CA1 to epileptic seizures.

Inhibitory Circuit Motifs

Inhibitory circuits perform different functions [5]. Afferent excitatory fibers (from other subfields) often terminate both on excitatory and inhibitory postsynaptic cells. If the inhibitory cells in turn provide inhibition to the excitatory pyramidal cells, the effect of incoming excitatory input on the postsynaptic excitatory cells is both excitatory (monosynaptic, one direct excitatory synapse) and inhibitory (disynaptic, IPSP originates from inhibitory interneuron that receives EPSP from afferent fiber). For this circuit to be effective, the inhibitory interneurons need to receive sufficient input (and be excitable enough) to fire action potentials in response to afferent input. In this case, the postsynaptic excitatory cell receives an EPSP immediately followed by an inhibitory postsynaptic potential (IPSP), with the delay between the two event onsets resulting from the extra synapse in the inhibitory branch of the circuit. This feedforward inhibitory circuit is present in many brain structures and has been extensively studied in the hippocampus. In this circuit, the Schaffer collaterals represent the afferent fibers to both the CA1 pyramidal cell and to soma-targeting, fast-spiking inhibitory interneurons. When activated, these interneurons strongly inhibit the pyramidal cells because of the proximity of their axonal terminals to the action potential initiation site in the pyramidal cell. There is a short delay (a few milliseconds) between arrival of the EPSP and the IPSP in the pyramidal cell (Fig. 8.8). This delay creates a short window of opportunity for the pyramidal cell to fire an action potential in response to the afferent input. Thus feedforward inhibition enforces precise *spike timing*. In the absence of such feedforward inhibition, EPSPs could be integrated (only limited by the relatively long time constant of the postsynaptic pyramidal cell) and produce spiking responses with low temporal precision. Thus feedforward inhibition turns pyramidal cells that are integrators of synaptic input into coincidence detectors that only fire in response to multiple inputs arriving almost at the same time (to sufficiently depolarize the postsynaptic cell before it is subjected to feedforward inhibition).

Feedforward inhibition also mediates *gain control*. Gain denotes the amplification of incoming input to form an output. Neuronal circuits need to be able to respond to input strengths that can span many orders of magnitude. This is most obvious for sensory systems that need to process a range of stimuli from very weak to very strong (eg, in terms of brightness in the visual system). In other words, circuits need to be responsive to extremely weak input, but at the same time not saturate for strong input such that strong inputs can still be distinguished. Feedforward inhibition provides such a mechanism, since the activation of the inhibitory pathway in the circuit depends on afferent input strength. For weak inputs,

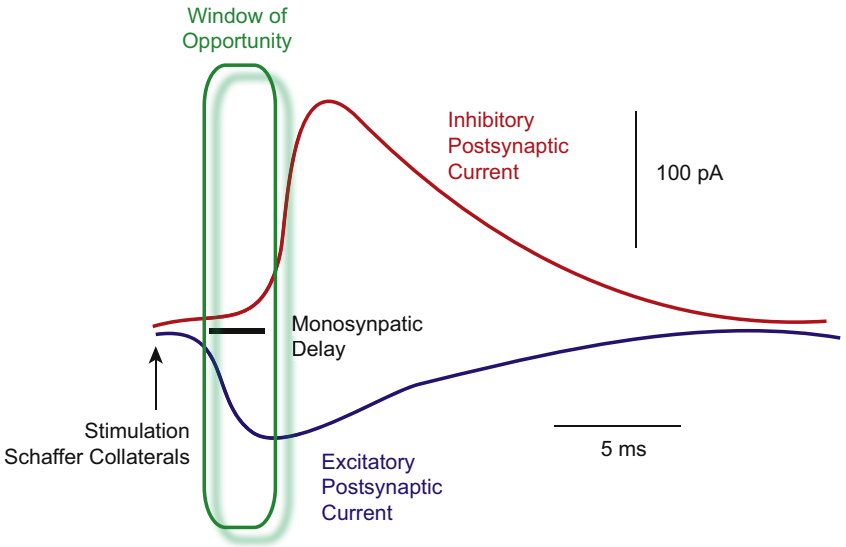

FIGURE 8.8 Feedforward inhibition. Synaptic currents in the pyramidal cell. Red: Inhibitory postsynaptic current (IPSC). Blue: Excitatory postsynaptic current (EPSC). Synaptic inputs are elicited by electrical stimulation of the afferent Schaffer collaterals. Green: Window of opportunity for firing an action potential. *Adapted from Pouille F, Scanziani M. Enforcement of temporal fidelity in pyramidal cells by somatic feed-forward inhibition. Science 2001;293(5532):1159–63.*

inhibition is barely activated and the excitatory input to the postsynaptic pyramidal cells is accordingly unhindered. In the case of strong afferent input, however, inhibition is recruited and makes it harder for the afferent excitatory input to make the postsynaptic pyramidal cells fire action potentials. Together, feedforward inhibition provides both fundamental temporal and spatial processing capabilities to local circuits.

Feedback inhibition denotes a related circuit motif in which activity of pyramidal cells in a given area synapses onto inhibitory interneurons that synapse onto the same pyramidal cell population. The main distinguishing features of feedback inhibition are (1) the population of pyramidal cells needs to be active to trigger and thus receive inhibition and (2) the excitation of the inhibitory cells is locally generated and not provided by a distant cell population. At the most basic level, feedback inhibition limits network activity by recruiting inhibition as a function of the activity of the pyramidal cells. This helps to prevent unwanted, elevated activity.

Inhibitory feedback loops can also contribute to shaping the temporal structure of activity. The dynamics of each loop are a function of the properties of the excitatory synapse onto the inhibitory interneuron, the intrinsic excitability of the interneuron, and the inhibitory synapse back onto the pyramidal cell. For example, in hippocampus CA1 there are two distinct feedback loops mediated by two types of functionally distinct inhibitory interneuron; these loops are recruited in a distinct manner and therefore provide different signal processing capabilities [7]. The first loop is activated by the onset of a train of action potentials in the pyramidal cells and provides perisomatic inhibition. Synaptic depression of the excitatory synapses on

these inhibitory interneurons quickly reduces the strength of the inhibition in case of sustained neuronal firing. The second loop is preferentially activated by sustained activity, since the excitatory synapses on this functional class of interneurons exhibit facilitation (see chapter: Synaptic Plasticity). These inhibitory interneurons provide inhibition to the more distal dendrites of the pyramidal cells. The differential targeting of the pyramidal cells in terms of the location of the synapses along the dendritic tree is important because the incoming inhibition interacts with different aspects of the electric signaling in the postsynaptic pyramidal cell. In particular, perisomatic inhibition regulates spike timing (conceptually similar to the feedforward inhibition discussed earlier) and may therefore be important for synchronization and the generation of oscillations. On the other hand, it is likely that inhibition of distal dendrites (electrically far from the soma) preferentially interacts with other excitatory inputs received by that part of the dendritic tree. The third and last inhibitory circuit motif is *mutual inhibition*, in essence the inhibitory counterpart to mutual excitation. Overall (in the hippocampus), inhibitory interneurons are far more likely to target principal cells than other interneurons. However, several classes of interneurons preferentially inhibit interneurons of the same class. Also there are populations of inhibitory interneurons that only inhibit other interneurons and do not target pyramidal cells. Mutual inhibition appears to be an important mechanism that contributes to the genesis of gamma oscillations by synchronized release of inhibition from pyramidal cells (see chapter: Gamma Oscillations).

SUMMARY AND OUTLOOK

In this chapter we reviewed the basic layout of the hippocampal circuits. The entorhinal cortex projects to the dentate gyrus, which connects to CA3, which in turn connects to CA1. The subiculum is the main target of the outputs of CA1 and projects back to the entorhinal cortex. The stereotyped layout of the different pathways within the (rodent) hippocampus greatly facilitates the study of synaptic connections and the microcircuits they form. In particular, the relative lack of recurrent excitation in CA1 makes that hippocampal field an ideal model system for understanding how incoming information interacts and gives rise to output in the absence of endogenous network dynamics.

The previously discussed circuit layout of the hippocampal formation also applies in principle to other species such as monkeys and humans, but major differences in terms of the anatomy have been noted. Most prominently, the CA1 pyramidal cell layer in primates is much thicker than in rodents (up to 30 cell bodies thick in humans). Also, as opposed to rodents, human granule cells have basal dendrites. Although the functional implications of these differences are unknown, these differences are important to note.

NOTES

- An authoritative and comprehensive discussion of the hippocampus is provided in *The Hippocampus Book* edited by Andersen, Morris, Amaral, Bliss, and O'Keefe [8].

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