THE SYNAPTIC ORGANIZATION OF THE BRAIN

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HIPPOCAMPUS

DANIEL JOHNSTON AND DAVID G. AMARAL

The hippocampus is one of the most thoroughly studied areas of the mammalian central nervous system. There are two main reasons for this. First, it has a distinctive and readily identifiable structure at both the gross and histological levels. The unusual shape of the human hippocampus resembles that of a sea horse, which is what led to its most common name (in Greek *hippo* means "horse" and *kampos* means "sea monster"). The hippocampus is also sometimes called Ammon's horn due to its resemblance to a ram's horn (the Egyptian god Ammon had ram's horns). But it is the histology of the hippocampus that makes it so seductive to neuroscientists. The hippocampus is beautifully laminated; both the neuronal cell bodies and the zones of connectivity are arranged in orderly layers. The hippocampus is one of a group of structures within the limbic system typically called the *hippocampal formation* that includes the dentate gyrus, the hippocampus, the subiculum, presubiculum and parasubiculum, and the entorhinal cortex. The dentate gyrus, hippocampus, and subiculum have a single cell layer with less cellular or acellular layers located above and below it. The other parts of the hippocampal formation have several cellular layers. The highly laminar nature of the dentate gyrus and hippocampus lends them to neuroanatomical and electrophysiological studies.

A second reason for the interest in the hippocampus is that since the early 1950s, it has been recognized to play a fundamental role in some forms of learning and memory. In a landmark paper by Scoville and Milner (1957), the neuropsychological findings from a patient known by his initials, H.M., who underwent bilateral hippocampal removal for the treatment of intractable epilepsy, were reported. HM, probably the most thoroughly studied neuropsychological subject in memory research, suffered a permanent loss of the ability to encode new information into long-term memory. This anterograde memory impairment has been seen in other patients with bilateral damage restricted to the hippocampus (Zola-Morgan et al., 1986). The intense interest in understanding the brain mechanisms involved in learning and memory have helped foster research at the neuroanatomical, physiological, and behavior levels of analysis in the hippocampus. These studies have forged a strong theoretical link between the hippocampus and certain forms of memory (see Functional Synthesis below). The hippocampus is also of interest because of its high seizure susceptibility. It has the lowest seizure threshold of any brain region (Green, 1964). Most patients with epilepsy have seizures that involve the hip-

pocampus, and these seizures are often the most difficult to control medically. Portions of the hippocampal formation, particularly the entorhinal cortex, also appear to be prime targets for the pathology associated with Alzheimer's disease, and the hippocampus is very vulnerable to the effects of ischemia and anoxia.

The anatomical and functional organization of the hippocampus is of particular relevance to this text on the synaptic organization of the brain because in many ways the hippocampus has become a model system for studies of other cortical structures. Much of what is currently known about the physiology and pharmacology of synaptic transmission in the central nervous system has come from studies of the hippocampus. Because the largest portion of the physiological literature on the hippocampal formation deals with either the dentate gyrus or the hippocampus, we will devote most of our coverage to these structures and will focus mainly on the organization of the rat hippocampus.

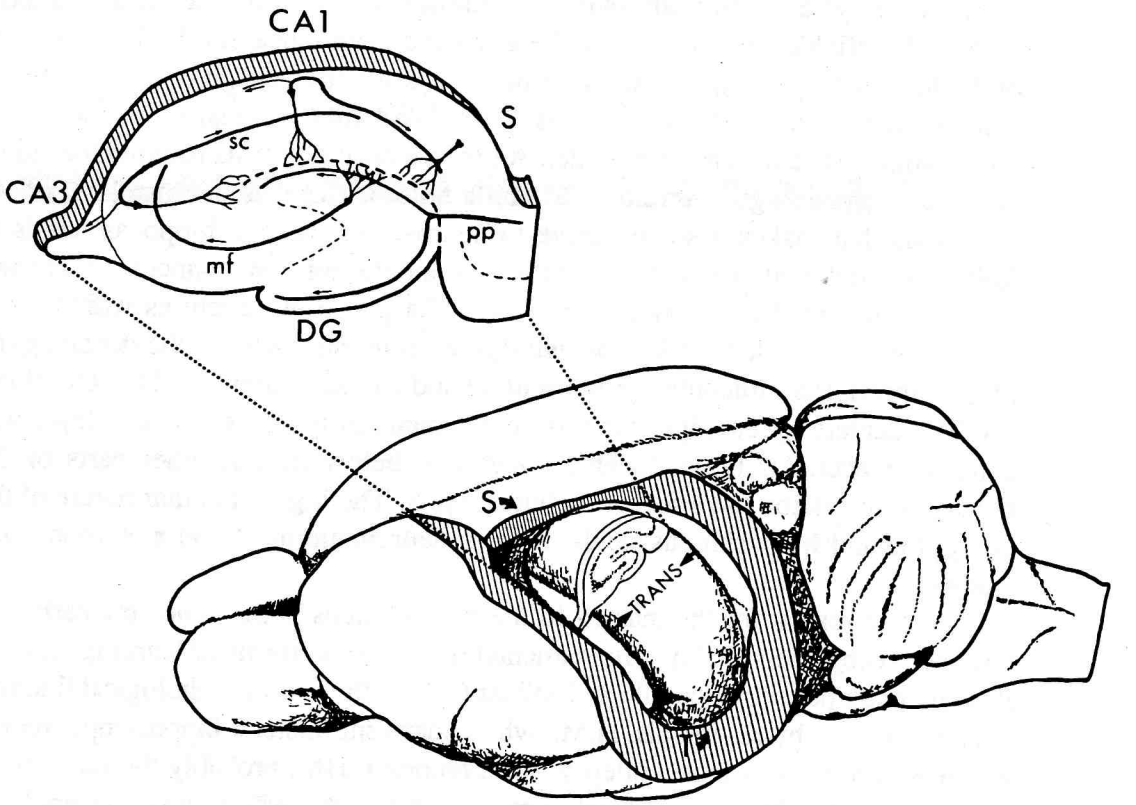

Fig. 11.1. Line drawing of a lateral cutaway view of the rat brain showing the location of the hippocampal formation (rostral is to the left and caudal is to the right). The hippocampus is a banana-shaped structure that extends from the septal nuclei rostrally to the temporal cortex, caudally. The long axis is called the *septotemporal axis* (indicated by S–T) and the orthogonal axis is the *transverse axis* (TRANS). A slice cut perpendicular to the long axis of the hippocampus (above left) shows several fields of the hippocampal formation and several of the intrinsic connections. Slices of this type are typically used for in vitro electrophysiological analyses of the hippocampus. Abbreviations: DG, dentate gyrus; CA3, CA1, fields of the hippocampus; S, subiculum; pp, perforant path fibers from the entorhinal cortex; mf, mossy fibers from the granule cells; sc, Schaffer collateral connections from CA3 to CA1. [From Amaral and Witter, 1989, with permission.]

NEURONAL ELEMENTS

THREE-DIMENSIONAL POSITION AND LAYERS OF THE RAT HIPPOCAMPUS

The three-dimensional position of the rat hippocampal formation in the brain is shown in Figure 11.1. It appears grossly as an elongated structure with its long axis extending in a C-shaped fashion from the septal nuclei rostrally, over and behind the diencephalon, into the temporal lobe caudally and ventrally. The long axis of the hippocampus is referred to as the *septotemporal axis* and the orthogonal axis is referred to as the *transverse axis*.

The various layers of the hippocampal formation are shown in Fig. 11.2. The dentate gyrus consists of three layers: the principal, or granule cell layer, the largely acellular molecular layer that is located above the granule cell layer, and the diffusely cellular polymorphic cell layer (also called the hilus) that is located below the granule cell layer. The hippocampus also has a principal cell layer called the *pyramidal cell layer*. The regions above and below the pyramidal cell layer are divided into a number of strata that we will describe in due course.

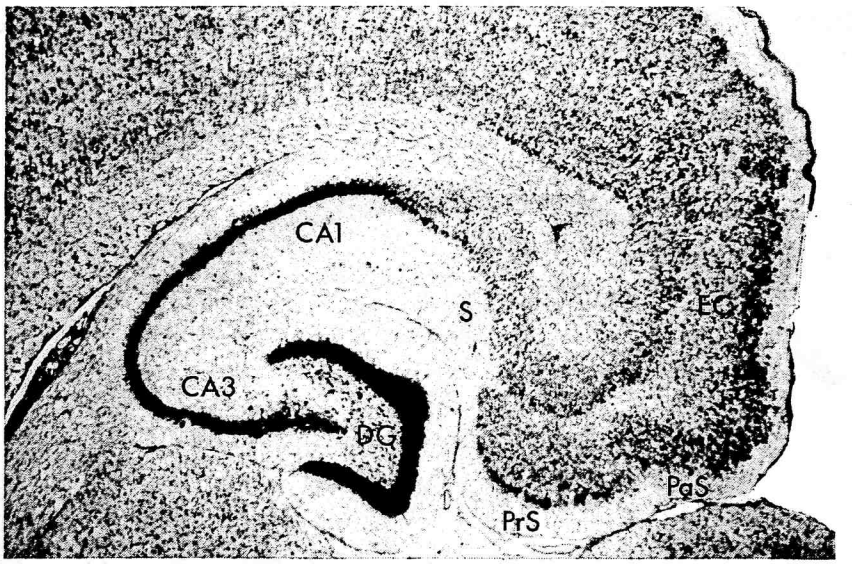

Fig. 11.2. A Nissl-stained horizontal section through the rat hippocampal formation showing all of its cytoarchitectonic divisions. (Caudal is to the right, rostral is to the left, and lateral is to the top.) The dark layers contain stained cell bodies. The acellular regions contain dendrites of the hippocampal neurons and axons from intrinsic and extrinsic sources. The dentate gyrus (DG) has three layers: the molecular layer (m); the granule cell layer (g) and the polymorphic cell layer (pl). The hippocampus is divided into CA3, CA2, and CA1 regions (CA2 not shown). In all hippocampal fields, the surface is formed by the alveus, a thin sheet of outgoing and incoming fibers. The layer occupied by basal dendrites of the pyramidal cells is stratum oriens (o) followed by the pyramidal cell layer (p) where the cell bodies of the pyramidal cells are located. Superficial to the pyramidal cell layer is stratum radiatum (r) and stratum lacunosum-moleculare (l-m) where the apical dendrites of the pyramidal cells are located. The subiculum (S), presubiculum (PrS), parasubiculum (PaS) and entorhinal cortex (EC) are also illustrated. A major input–output fiber bundle is the fimbria (f). The angular bundle (ab) is a fiber region in which the perforant path fibers travel from the entorhinal cortex to the other fields of the hippocampal formation.

PRINCIPAL NEURONS

The principal neurons in the dentate gyrus are the *granule cells*, and in the hippocampus they are the *pyramidal neurons*. The pyramidal cell layer of the hippocampus has been divided into three regions designated *CA1–CA3* (Lorente de Nó, 1934) based on the size and appearance of the neurons.

The granule cells have small (about 10 μm in diameter), spherically shaped cell bodies that are arranged 4–6 cells thick in the *granule cell layer*. In rodents, the granule cell layer is shaped like the letter "V" or "U," depending on the septotemporal level (see Fig. 11.3). The granule cell dendrites extend perpendicularly to the *granule cell layer*, into the overlying *molecular layer* where they receive synaptic connections from several sources. Because the dendrites emerge only from the top or apical portion of the cell body, granule cells are considered to be monopolar neurons. The axons of the granule cells are called *mossy fibers* because of the peculiar appearance of their synaptic terminals. They typically originate from the basal portion of the cell body, i.e., opposite to where the dendrites originate, and extend into the *polymorphic cell layer* (also called the *hilus*). The mossy fibers synapse onto some of the neurons, such as mossy cells, in the polymorphic cell layer before coalescing into a bundle of fibers that exits the hilus and enters stratum lucidum of CA3. The polymorphic cells are, as the name implies, of various types but they only project to other parts of the dentate gyrus.

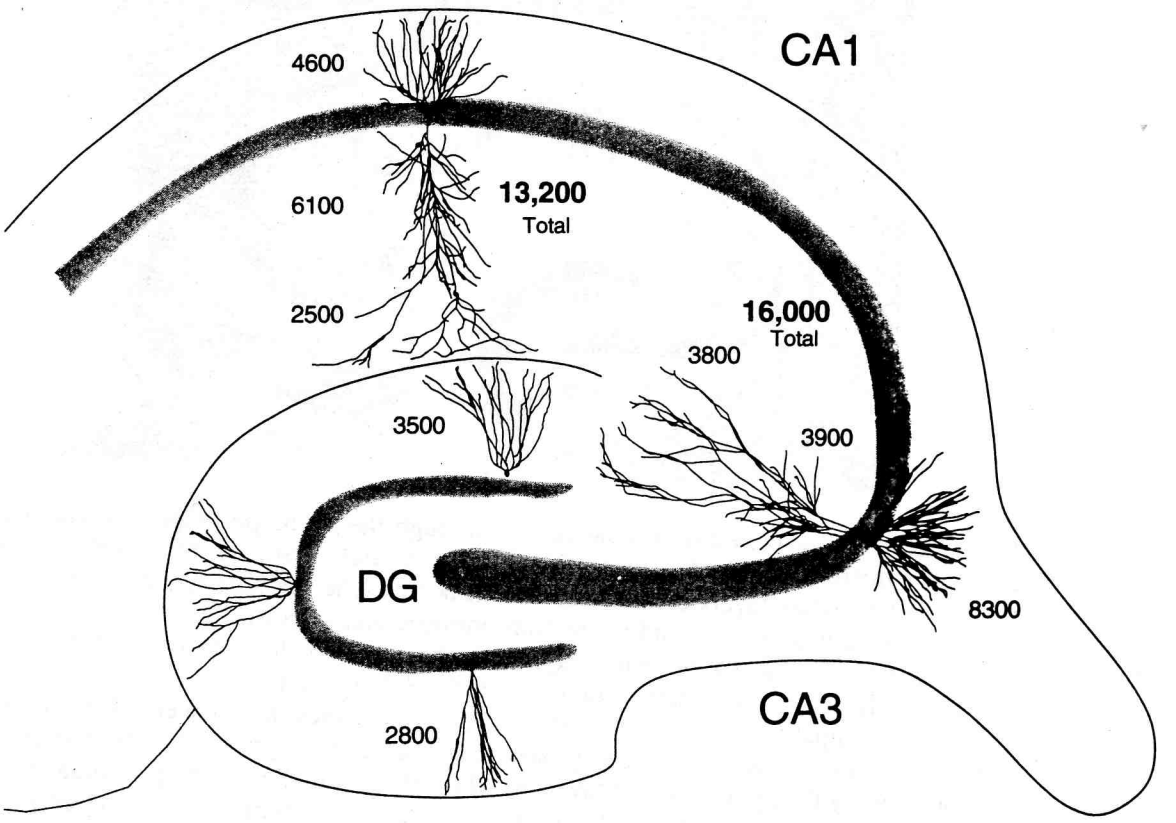

Fig. 11.3. Line drawing showing the shape and size of the principal neurons in the dentate gyrus (DG) and hippocampus (CA3 and CA1). Numbers indicate the total dendritic length of granule cells and of the portions of the dendritic trees located in stratum lacunosum-moleculare, radiatum, and oriens of the hippocampus. For the hippocampal cells, the total dendritic lengths are also given.

The cell bodies of the hippocampal pyramidal neurons are arranged, 3–6 cells deep, in an orderly layer called the *pyramidal cell layer*. These neurons have elaborate dendritic trees extending perpendicularly to the cell layer in both directions and are thus considered to be multipolar neurons but more typically called *pyramidal cells*. The apical dendrites are longer than the basal and extend from the apex of the pyramidal cell body toward the center of the hippocampus, i.e., towards the dentate gyrus (Fig. 11.3). The apical dendrites of CA3 pyramidal cells traverse three strata: stratum lucidum, strata radiatum, and stratum lacunosum-moleculare. The dendrites receive different types of synaptic contacts in each one of these strata. The basal dendrites extend from the base of the pyramidal cell body into stratum oriens.

The hippocampus can clearly be divided into two major regions, a large-celled region closer to the dentate gyrus and a smaller-celled distal region. Ramon y Cajal (1911) called these two regions *regio inferior* and *regio superior*, respectively. However, as noted above, Lorente de Nó (1934), divided the hippocampus into three fields (CA3, CA2, and CA1). He also used the term *CA4*, although this referred to the region occupied by the polymorphic layer of the dentate gyrus; CA4 is typically no longer used. His CA3 and CA2 fields are equivalent to the large-celled regio inferior of Ramon y Cajal and his CA1 is equivalent to regio superior. In addition to differences in the size of the pyramidal cells in CA3 and CA1, there is a clear-cut connectional difference. The CA3 pyramidal cells receive a mossy fiber input from the dentate gyrus and the CA1 pyramidal cells do not.

The CA2 field has been a matter of some controversy. As originally defined by Lorente de Nó, it was a narrow zone of cells interposed between CA3 and CA1, which had large cell bodies like CA3 but did not receive mossy fiber innervation like CA1 cells. The bulk of available evidence indicates that there is, indeed, a narrow CA2 which has both connectional and perhaps even functional differences with the other hippocampal fields. CA2, for example, appears to be more resistant to epileptic cell death than CA3 or CA1 and is sometimes referred to as the *resistant sector* Corsellis and Bruton (1983).

The dendrites of the pyramidal neurons are covered with spines onto which most excitatory synapses terminate. Some of the largest spines in the nervous system are the thorny excrescences, which are located on the proximal dendrites of CA3 and receive the synapses of the mossy fibers. The thorny excrescences are complex branched spines engulfed by a single mossy-fiber bouton (Hamlyn, 1962; see below). The remainder of the dendritic tree of CA3 pyramidal cells and the entire CA1 pyramidal cell dendritic tree have standard "cortical-like" spines on which excitatory, asymmetric synapses are formed.

INTERNEURONS

Intrinsic neurons, or interneurons, have traditionally been defined as neurons with a locally restricted axon plexus that lack spines and release γ-amino butyric acid (GABA). Recently, with advances in cell labeling, staining, and recording, interneurons have been found to be much more diverse than previously thought, and exceptions to all of these traditional views have been described (Buckmaster and Soltesz, 1996).

The vast majority of interneurons in the dentate gyrus and hippocampus (Fig. 11.4) do indeed have locally restricted target regions, lack spines, and are GABAergic

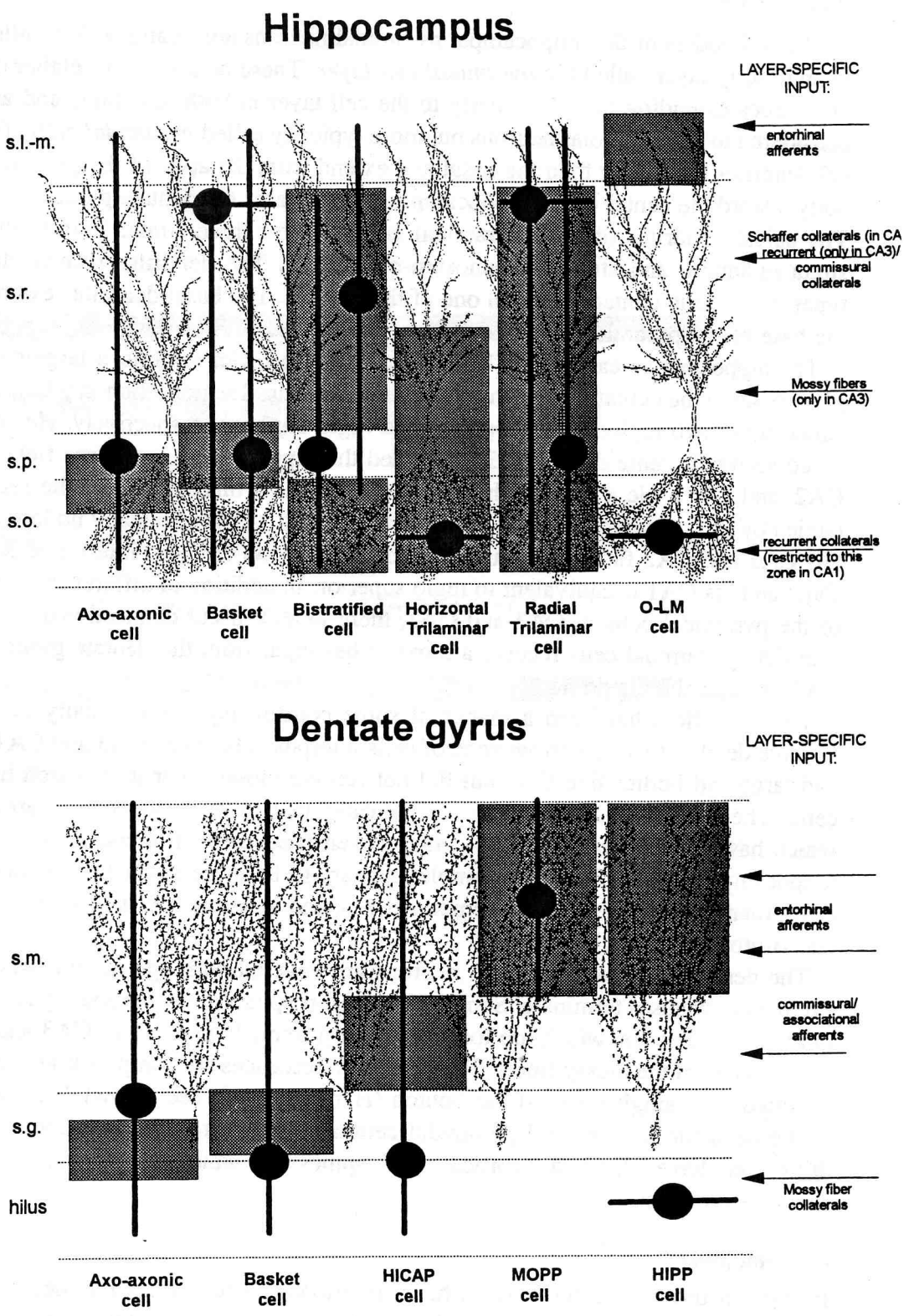

Fig. 11.4. A summary diagram of the various interneurons in the hippocampus and dentate gyrus. Most of the interneurons use GABA as their transmitter. Light profiles in the background show pyramidal cells (in the hippocampus) and granule cells (in the dentate gyrus). The interneurons innervate different portions of these principal neurons. For the interneurons, the locations of the cell bodies are marked with circles. The dark lines emanating from the circles represent the orientation and the laminar location of the major dendrites. The hatched area marks the regions where the axons from each interneuron typically arborizes. The laminar distribution of several of the excitatory inputs to these fields are indicated at right. [From Freund and Buzsaki, 1996, with permission.]

(Freund and Buzsaki, 1996.) In the dentate gyrus, the most prominent class of interneurons is called the *pyramidal basket cell* and the cell bodies of these neurons are typically located at the border between the granule cell layer and the polymorphic cell layer. Axons from these neurons innervate the cell bodies of granule cells. There are at least five different types of these basket cells (Ribak and Seress, 1983). There are also interneurons in the molecular layer. Perhaps the most interesting of these is an axo-axonic cell that terminates on the axon initial segments of granule cells (Kosaka, 1983; Freund and Buzsaki, 1996). There is also a variety of interneurons located in the polymorphic cell layer. Some of these have axons that remain within the polymorphic cell layer while others innervate the granule and molecular layers (Freund and Buzsaki, 1996). There is a class of neurons in the polymorphic layer that are called *mossy cells* (Amaral, 1978). These are excitatory neurons that nonetheless project only to the molecular layer of the dentate gyrus both ipsilaterally and contralaterally. Whereas some investigators have called these *excitatory interneurons*, the fact that they project their axons for long distances on both sides of the hippocampus would seem to preclude the use of the term interneuron. In fact, these neurons tend not to project locally but rather to distant septotemporal levels of the dentate gyrus. These types of neurons would then form an exception to the traditional definitions of interneurons and principal neurons.

Hippocampal interneurons with cell bodies in or near the pyramidal cell layer can be classified into three groups on the basis of their synaptic targets: axo-axonic cells, basket cells, and bistratified cells. As the name implies, *axo-axonic cells* synapse onto the initial segments of pyramidal neurons and thus exert a strong control over action potential initiation. *Basket cells* synapse onto the somata of pyramidal neurons. Each basket cell can make multiple contacts onto a pyramidal neuron, forming what looks like a "basket" into which the soma sits. Finally, *bistratified cells* make synaptic contacts onto apical and basal dendrites of pyramidal neurons. Although there is very little overlap among their target regions, the dendrites of all three cell types project into stratum radiatum and stratum oriens and thus may receive excitatory inputs from Schaffer collaterals, commissural-associational fibers, and feedback synapses from pyramidal neurons in the local region of the interneurons (Buhl et al., 1996; Halasy et al., 1996). There are also mutual inhibitory connections among these interneurons. The mutual inhibitory connections are thought to synchronize the interneurons producing oscillations at various frequencies, including theta (5 Hz) and gamma (40 Hz) frequencies (Jefferys et al., 1996). Many GABAergic interneurons also contain and release neuroactive peptides (see Freund and Buzsaki, 1996, for review).

There are also GABAergic interneurons in stratum radiatum and stratum lacunosum-moleculare which receive excitatory inputs from Schaffer collaterals and perforant path fibers, respectively, and synapse onto pyramidal neuron dendrites in various regions. Among interneurons whose properties and connections are less well known are putative excitatory interneurons in stratum lucidum that receive input from mossy fibers and synapse onto CA3 pyramidal neurons (Soriano and Frotscher, 1993), and interneurons whose postsynaptic targets are exclusively other interneurons (Freund and Buzsaki, 1996).

BASIC CIRCUITS

The basic circuitry of the hippocampal formation has been known since the time of Ramon y Cajal (1911), although details worked out by modern neuroanatomists have

contributed to our current understanding, which is illustrated schematically in Fig. 11.5. Andersen and colleagues (1971) emphasized the unique unidirectional progression of excitatory pathways that linked each region of the hippocampal formation and coined the term *trisynaptic circuit*. For simplicity, the entorhinal cortex is considered to be the starting point of the circuit since much of the sensory information that reaches the hippocampus enters through the entorhinal cortex.

Neurons located in layer II of the entorhinal cortex give rise to a pathway, the *perforant path*, that projects through (perforates) the subiculum and terminates both in the dentate gyrus and in the CA3 field of the hippocampus. Cells in the medial entorhinal cortex contribute axons that terminate in a highly restricted fashion within the middle portion of the molecular layer of the dentate gyrus and those from the lateral entorhinal cortex terminate in the outer third of the molecular layer. These two components of the perforant path also end in a laminar pattern in the stratum lacunosum-moleculare of CA3 and CA2. Neurons located in layer III of the entorhinal cortex do not project to the dentate gyrus or CA3 but do project to CA1 and the subiculum. In this case, the projection is not organized in a laminar fashion but rather in a topographic fashion. Axons originating from neurons in the lateral entorhinal cortex terminate in that portion of stratum lacunosum-moleculare located at the border of CA1 with the subiculum. Projections arising from the medial entorhinal cortex terminate in that portion of stratum lacunosum-moleculare of CA1 that is located close to CA3 and in the molecular layer of the subiculum located close to the presubiculum.

The dentate gyrus is the next step in the progression of connections, and it gives rise to the mossy fibers that terminate on the proximal dendrites of the CA3 pyramidal cells. The granule cells also synapse on cells of the polymorphic layer, which provides associ-

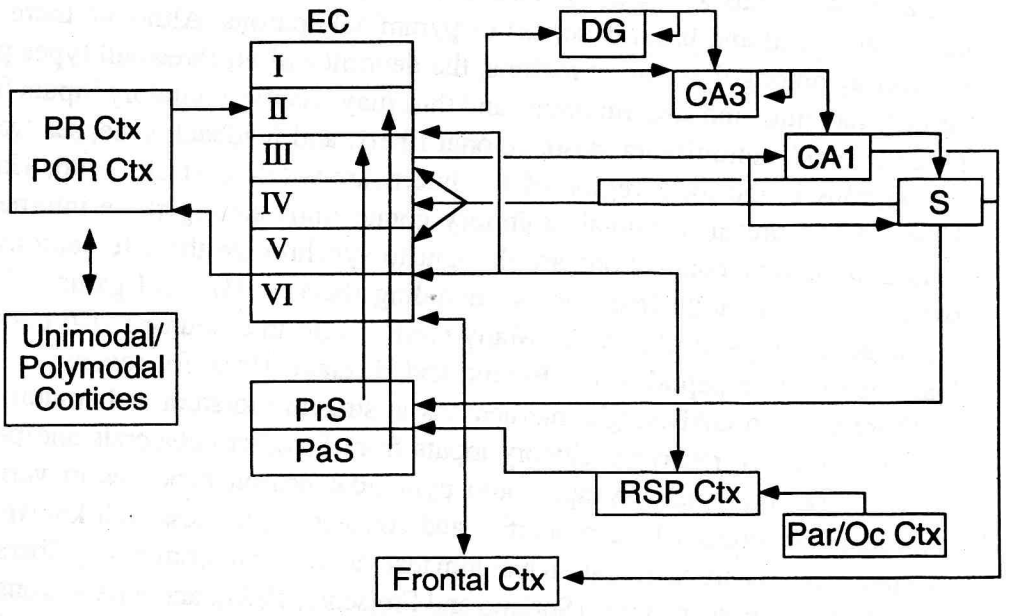

Fig. 11.5. Summary diagram of the major intrinsic connections of the rat hippocampal formation and several of the extrinsic cortical inputs. This diagram emphasizes the serial and parallel aspects of the intrinsic hippocampal circuitry. See text. Abbreviations: DG, dentate gyrus; CA3, CA1 fields of the hippocampus; EC, entorhinal cortex; PR, perirhinal; POR, postrhinal; PrS, presubiculum; PaS, parasubiculum; Par/Oc Ctx, parietal occipital cortices; RSP Ctx, retrosplenial cortex.

ational connections to other levels of the dentate gyrus.The CA3 pyramidal cells, in turn, project heavily to other levels of CA3 as well as to CA1. The projection to CA1 is typically called the *Schaffer collateral projection.* CA1 pyramidal cells give rise to connections both to the subiculum and to the deep layers of the entorhinal cortex. The subiculum also originates a projection to the deep layers of the entorhinal cortex. The deep layers of the entorhinal cortex, in turn, originate projections to many of the same cortical areas that originally projected to the entorhinal cortex. Thus, information entering the entorhinal cortex from a particular cortical area can traverse the entire hippocampal circuit through the excitatory pathways just described and ultimately be returned to the cortical area from which it originated. The transformations that take place through this traversal are presumably essential for enabling the information to be stored as long-term memories.

Now that the basic framework of the connectivity of the hippocampal formation has been layed out, we will delve more deeply into the synaptic organization of the dentate gyrus and hippocampus.

SYNAPTIC CONNECTIONS OF THE DENTATE GYRUS

The dentate granule cells give rise to the distinctive unmyelinated axons called *mossy fibers* (Fig. 11.6). Each mossy fiber gives rise to about seven thinner collaterals within the polymorphic layer before entering the CA3 field of the hippocampus (Claiborne et al., 1986). Within the polymorphic layer, the mossy fiber collaterals have two types of synaptic varicosities. There are about 160 small (0.5–2 μm) varicosities that form contacts on spines and dendritic shafts of polymorphic layer neurons (Claiborne et al.,

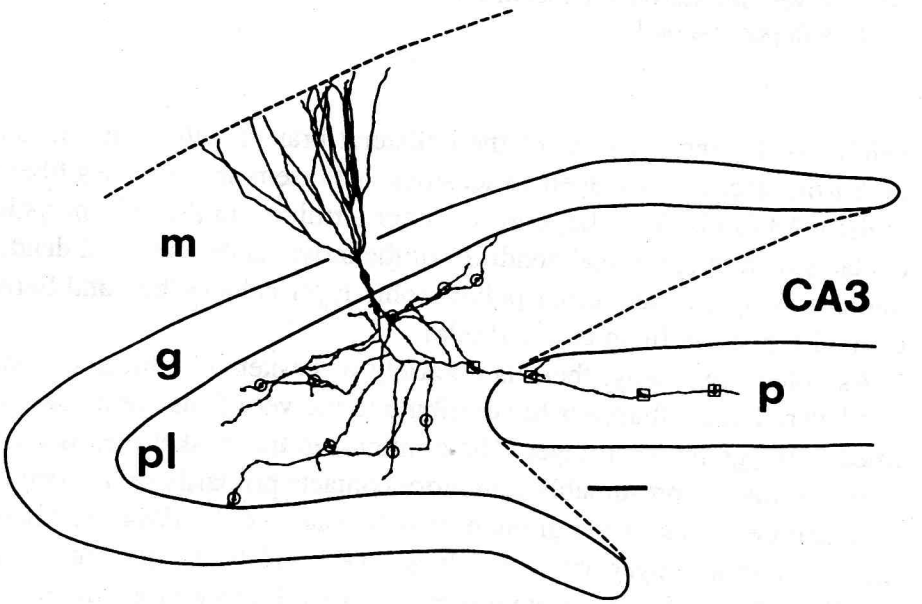

Fig. 11.6. Line drawing of a dentate granule cell and its mossy fiber axonal plexus. The axon originates from the cell body and descends into the polymorphic layer (pl) where it collateralizes. Each collateral has many small synaptic varicosities (small dots) and usually one larger presynaptic terminal (circles) that resemble the mossy fiber expansions found in stratum lucidum. The main mossy fiber axon enters CA3 and demonstrates several en passant and very large (3–8 μm) expansions (boxes) as it traverses the entire CA3 field before entering stratum lucidum. m, molecular layer; g, granule cell layer; p, pyramidal cell layer, pl, polymorphic layer.

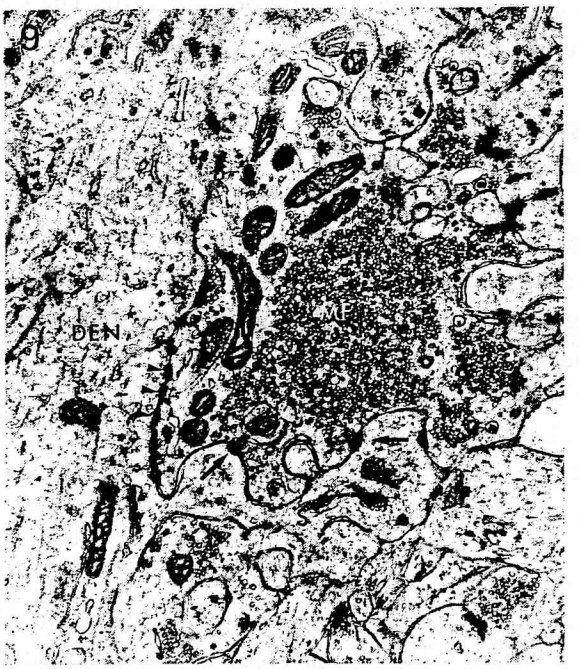

Fig. 11.7. Electron micrograph of a mossy fiber expansion (MF) that makes contact with a pyramidal cell dendrite (DEN). A large, complex thorny excrescence (S) is shown penetrating the expansion. There are several symmetrical contacts between the dendritic shaft and the expansion (arrowheads) which are nonsynaptic puncta adhearentia. There are also several asymmetric synapses between the expansions and the complex spine (arrows). Note that the small, round synaptic vesicles are only associated with the spine specializations. [From Amaral and Dent, 1981, with permission.]

1986). At the ends of each of the collateral branches there are usually single, larger (3–5 μm), irregularly shaped varicosities that resemble the mossy fiber terminals found in the CA3 field. These large mossy fiber terminals in the polymorphic layer establish contacts with the proximal dendrites of the mossy cells, the basal dendrites of the pyramidal basket cells, and other polymorphic layer cells (Ribak and Seress, 1983; Ribak et al., 1985; Scharfman et al., 1990a).

As noted previously, there is a variety of basket cells located close to the granule cell layer. These all appear to contribute to the very dense terminal plexus that is confined to the granule cell layer. The terminals in this basket plexus are GABAergic and form symmetric, presumably inhibitory contacts primarily on the cell bodies and shafts of apical dendrites of the granule cells (Kosaka et al., 1984). GABAergic neurons in the polymorphic layer are themselves innervated by GABAergic terminals (Misgeld and Frotscher, 1986). How widespread is the influence of a single basket cell? Analysis of Golgi-stained axonal plexuses from single basket cells (Struble et al., 1978) indicates that they extend on average 400 μm in the transverse axis and at least 1.1 mm in the septotemporal axis. It is conceivable, therefore, that a single basket cell has influence over a very large number of granule cells.

A second inhibitory input to granule cells originates from the axo-axonic or "chandelier-type" cells located in the molecular layer (Kosaka, 1983; Soriano and Frotscher, 1989). These form symmetric contacts exclusively with the axon initial segment of

granule cells. Another intrinsic projection within the dentate gyrus arises from a population of somatostatin immunoreactive neurons scattered throughout the polymorphic layer (Morrison et al., 1982; Bakst et al., 1986). These somatostatin cells, located in the polymorphic layer, colocalize GABA and contribute a plexus of fibers and terminals to the outer portions of the molecular layer. This system of fibers, which forms contacts on the distal dendrites of the granule cells, provides a third means for inhibitory control over granule cell activity (Freund and Buzsaki, 1996).

The inner third of the molecular layer of the dentate gyrus receives a projection that originates exclusively from cells in the polymorphic layer (Blackstad, 1956; Laurberg and Sorensen, 1981). Since this projection originates both on the ipsilateral and contralateral sides, it has been called the *ipsilateral associational/commissural projection.* The ipsilateral associational and commissural projections appear to originate as collaterals from axons of the mossy cells of the hilus (Laurberg and Sorensen, 1981). Most terminals of this pathway form asymmetric, presumably excitatory synaptic terminals on spines of the granule cell dendrites (Laatsch and Cowan, 1967; Kishi et al., 1980). Since the mossy cells are immunoreactive for glutamate (Soriano and Frotscher, 1993), it is likely that they release this excitatory transmitter substance at their terminals within the ipsilateral associational/commissural zone of the molecular layer.

Since the mossy cells are densely innervated by the granule cells, they provide the substrate for a potential feedback loop via their axons to the proximal dendrites of the granule cells. However, a few facts temper the way we think about this feedback loop. The granule cells innervate mossy cells at the same septotemporal level at which their cell bodies are located. However, the mossy cells project not to the same level that their cell bodies are located but to distant levels located both septally and temporally from the level of the cell body. Thus, it would appear that the mossy cells pass on the collective output of granule cells from one septotemporal level to granule cells located at distant levels of the dentate gyrus. The functional significance of the longitudinal distribution of the associational projection cannot be fully appreciated without one further piece of information. In addition to contacting the spines of dentate granule cells, the associational fibers also contact the dendritic shafts of GABAergic basket cells (Frotscher and Zimmer, 1983; Seress and Ribak, 1984). Thus, the associational and commissural projections may function both as a feedforward excitatory pathway and as a disynaptic feedforward inhibitory pathway. A final fact that contributes to this discussion is that the somatostatin/GABA pathway described above (which originates from cells in the polymorphic layer) has a more local and limited terminal distribution. Thus, mossy fiber collaterals terminating on GABA/somatostatin cells in the polymorphic layer may lead predominantly to direct inhibition of granule cells at the same septotemporal level and to either inhibition or excitation (via the ipsilateral associational connection) at more distant levels of the dentate gyrus. The fact that the ipsilateral associational connection appears to be organized primarily to influence cells some distance away from the cell bodies of origin is a significant contradiction to the notion that the hippocampus processes information exclusively in a lamellar fashion, i.e., within slices of the hippocampal banana (Amaral and Witter, 1989).

Synaptic Connections from the Entorhinal Cortex. The major input to the dentate gyrus is from the entorhinal cortex. The major organizational features of this projection have

already been described. The projection to the dentate gyrus arises mainly from layer II of the entorhinal cortex (Steward and Scoville, 1976; Schwartz and Coleman, 1981; Ruth et al., 1982, 1988). A minor component of the projection also comes from the deep layers (IV–VI) of the entorhinal cortex (Köhler, 1985). In the molecular layer of the dentate gyrus, the terminals of the perforant path fibers are strictly confined to the outer or superficial two-thirds, where they form asymmetric synapses (Nafstad, 1967). These occur most frequently on the dendritic spines of dentate granule cells, although a small proportion of perforant path fibers terminate on the basket pyramidal interneurons (Zipp et al., 1989). Within the outer two-thirds of the molecular layer, perforant path synapses make up at least 85% of the total synaptic population (Nafstad, 1967). The perforant path is most likely glutamatergic (Fonnum et al., 1979). At least for the projection to the dentate gyrus, the terminals of the lateral perforant pathway are enkephalin immunoreactive, whereas those of the medial pathway are immunoreactive for CCK (Fredens et al., 1984).

Extrinsic Inputs to the Dentate Gyrus. The remainder of this section will deal with the subcortical inputs to the dentate gyrus, which originate mainly from the septal nuclei, supramamillary region of the posterior hypothalamus, and several monoaminergic nuclei in the brainstem, especially the locus coeruleus and raphe nuclei.

The septal projection arises from cells of the medial septal nucleus and the nucleus of the diagonal band of Broca and travels to the hippocampal formation via four routes: the fimbria, dorsal fornix, supracallosal stria, and via a ventral route through and around the amygdaloid complex (Mosko et al., 1973; Swanson, 1978; Amaral and Kurz, 1985). Septal fibers heavily innervate the polymorphic layer, particularly in a narrow band just below the granule cell layer, and terminate more lightly in the molecular layer. Thirty to fifty percent of the cells in the medial septal nucleus and 50–75% of the cells in the nucleus of the diagonal band that project to the hippocampal formation are cholinergic (Amaral and Kurz, 1985; Wainer et al., 1985). Many of the other septal cells that project to the dentate gyrus, however, contain glutamic acid decarboxylase and are presumably GABAergic (Köhler et al., 1984); they terminate in the dentate gyrus and have an apparent preference for terminating on the GABAergic nonpyramidal cells (Freund and Antal, 1988). The septal GABAergic projection provides a striking example of long, projection neurons (not interneurons) that use GABA as their transmitter.

There is only one major hypothalamic projection to the dentate gyrus and this arises from the supramammillary area (Wyss et al., 1979a,b; Dent et al., 1983; Haglund et al., 1984). The supramamillary projection terminates heavily in a narrow zone of the molecular layer located just superficial to the granule cell layer; there is only light innervation of the polymorphic or molecular layers.

The dentate gyrus receives a particularly prominent noradrenergic input primarily from the locus coeruleus (Pickel et al., 1974; Swanson and Hartman, 1975), and the noradrenergic fibers terminate mainly in the polymorphic layer of the dentate gyrus. The serotonergic projection, which originates from the raphe nuclei, also terminates most heavily in the polymorphic layer, but the projection tends to be limited to an immediately subgranular portion of the layer (Conrad et al., 1974). Freund and colleagues

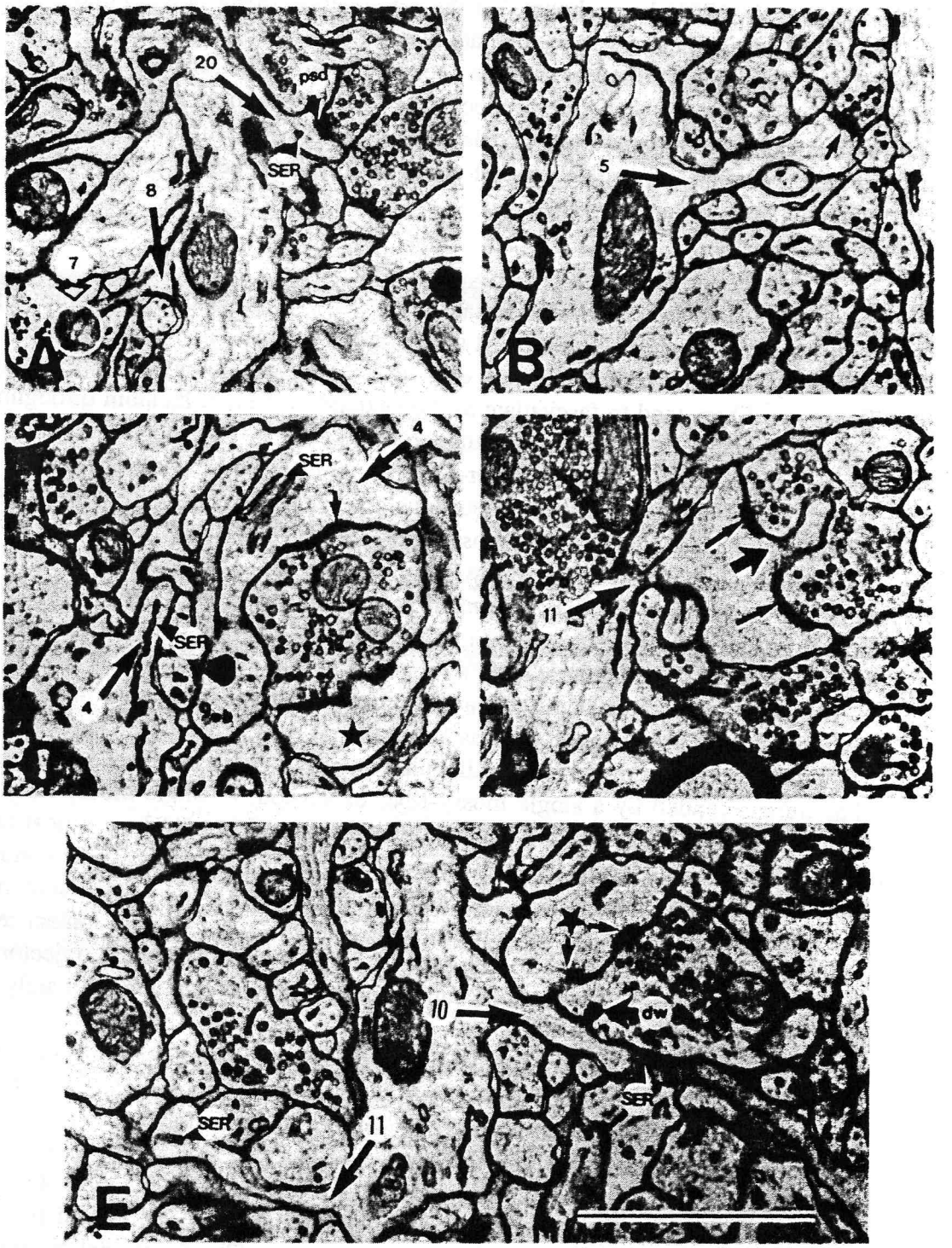

Fig. 11.8. Electron micrographs of axospinous synapses in the CA1 region of the rat hippocampus. **A:** A stubby spine (20) is identified and shows a postsynaptic density (psd). A cistern of smooth endoplasmic reticulum (ser) is in the spine. **B:** A typical thin spine with asymmetrical synapse on its head. **C:** Spine with large spine head making contact with axonal terminal. **D:** Perforated synapse. The spinule (large arrow) perforates the postsynaptic density which forms two patches (small arrows). **E:** Two very thin spine necks (10 and 11). [From Harris and Stevens, 1989, with permission.]

(Halasy et al., 1991) have shown that the serotonergic fibers preferentially terminate on a class of interneurons in the dentate gyrus that primarily innervate the distal dendrites of the granule cells. As with the cholinergic projection, many of the cells in the raphe nuclei that project to the hippocampal formation appear to be nonserotonergic (Köhler and Steinbusch, 1982). The dentate gyrus receives a lighter and diffusely distributed dopaminergic projection that arises mainly from cells located in the ventral tegmental area (Swanson, 1982).

Outputs of the Dentate Gyrus. The dentate gyrus does not project to other brain regions. Within the hippocampal formation, it only projects to CA3 via the mossy fibers. Once the mossy fibers leave the hilus and enter the CA3 region, they have few collaterals. The mossy fibers tend to fasciculate as they extend in stratum lucidum throughout the CA3 field, where they demonstrate the large (3–6 μm in diameter), presynaptic varicosities characteristic of mossy fiber–CA3 pyramidal cell contacts (Claiborne et al., 1986). These large, presynaptic expansions are distributed at approximately 140-μm intervals along the course of the mossy fiber axons. In the part of CA3 located closest to the dentate gyrus, some mossy fibers extend deep to the pyramidal cell layer in what has been called the *infrapyramidal bundle*. In this region, the mossy fibers terminate on large thorny excrescences that are located both on the proximal apical and basal dendrites of the pyramidal cells.

The mossy-fiber presynaptic expansion forms a unique synaptic complex with an equally intricate postsynaptic process called the *thorny excrescence* (Fig. 11.7). These spine-like processes are large, multilobulated entities (with as many as 16 branches) that are surrounded by a single mossy-fiber expansion. A single mossy-fiber expansion can make as many as 37 synaptic contacts with a single CA3 pyramidal-cell dendrite (Chicurel and Harris, 1992). Because of the large size and proximal dendritic location of the mossy fiber synapse, the granule cells are in a unique position to influence the activity of hippocampal pyramidal cells. However, mossy fibers contact relatively few pyramidal cells, perhaps no more than 14 throughout their entire trajectory (Claiborne et al., 1986). Each pyramidal cell receives contacts from approximately 50 dentate granule cells.

The mossy fibers remain at approximately the same septotemporal level as their cells of origin (Gaarskjaer, 1978a,b; Swanson et al., 1978; Claiborne et al., 1986). In this respect, they are different from the organization of the ipsilateral associational connection in the dentate gyrus and the connections of the hippocampus, which tend to have much more extensive septotemporal distributions. Near the CA3–CA2 border, however, the mossy fibers make an abrupt turn temporally and extend for 1 mm or more towards the temporal pole of the hippocampus. The functional significance of this component of the mossy fibers has never been understood.

The mossy fibers are thought to use glutamate (Storm-Mathisen and Fonnum, 1972) as their primary transmitter substance. But some mossy fibers harbor opiate peptides such as dynorphin and enkephalin (Gall et al., 1981; Gall, 1984; van Daal et al., 1989). More recently, mossy fibers have also been shown to be immunoreactive for GABA (Sloviter et al., 1996). However, it is not clear whether this is involved in synaptic transmission or has a more general metabolic role.

SYNAPTIC CONNECTIONS OF CA3

The CA3 pyramidal cells give rise to highly collateralized axons that distribute fibers both within the hippocampus (to CA3, CA2, and CA1), to the same fields in the contralateral hippocampus (the commissural projections), and subcortically to the lateral septal nucleus. CA3 cells, especially those located proximally in the field, and CA2 cells contribute a small number of collaterals that innervate the polymorphic layer of the dentate gyrus.

All of the CA3 and CA2 pyramidal cells give rise to highly divergent projections to all portions of the hippocampus (Ishizuka et al., 1990). The projections to CA3 and CA2 are typically called the *associational connections* and the CA3 projections to the CA1 field are called the *Schaffer collaterals*. There is a highly ordered and spatially distributed pattern of projections from CA3 to CA3 and from CA3 to CA1 (Ishizuka et al., 1990). The essential elements of the organization of these connections include the following.

All portions of CA3 and CA2 project to CA1 but the distribution of terminations in CA1 depends on the transverse location of the CA3/CA2 cells of origin. The older notion that a typical CA3 pyramidal cell sends a single axon to CA1 that extend linearly through the field with equal contact probability at all regions within CA1 is clearly incorrect. The topographic organization of projections from CA3 to CA1 determines a network in which certain CA3 cells are more likely to contact certain CA1 cells. CA3 cells located close to the dentate gyrus, while projecting both septally and temporally for substantial distances, tend to project more heavily to levels of CA1 located septal to their location. CA3 cells located closer to CA1, in contrast, project more heavily to levels of CA1 located temporally. At or close to the septotemporal level of the cells of origin, those cells located proximally in CA3 give rise to collaterals that tend to terminate superficially in stratum radiatum. Conversely, cells of origin located more distally in CA3 give rise to projections that terminate deeper in stratum radiatum and in stratum oriens. At or close to the septotemporal level of origin, CA3 pyramidal cells located near the dentate gyrus tend to project somewhat more heavily to distal portions of CA1 (near the subicular border), whereas CA3 projections arising from cells located distally in CA3 terminate more heavily in portions of CA1 located closer to the CA2 border.

Regardless of the septotemporal or transverse origin of a projection, the highest density of terminal and fiber labeling in CA1 shifts to deeper parts of stratum radiatum and stratum oriens at levels septal to the cells of origin and shifts out of stratum oriens and into superficial parts of stratum radiatum at levels temporal to the origin. Moreover, the highest density of fiber and terminal labeling in CA1 shifts proximally (towards CA3) at levels septal to the origin and distally (towards the subiculum) at levels temporal to the origin. While Schaffer collaterals are often illustrated as extending only through stratum radiatum, it should be emphasized that both stratum radiatum and stratum oriens of CA1 are heavily innervated by CA3 axons. Thus, the Schaffer collaterals are as highly associated with the apical dendrites of CA1 cells in stratum radiatum as they are with the basal dendrites in stratum oriens. Moreover, some Schaffer collaterals that are initially in stratum radiatum ultimately extend into stratum oriens, and thus these axons may terminate on the apical dendrites of some pyramidal cells and the basal dendrites of other pyramidal cells. Although it has been implicit in our

discussion of these connections, it should be emphasized that each CA3 neuron makes contacts with many CA1 pyramidal cells. It has been estimated, for example, that a single CA1 neuron may be innervated by more than 5,000 ipsilateral CA3 pyramidal cells (Amaral et al., 1990). The projections from CA3 to CA1 terminate as asymmetric, axospinous synapses located on the apical and basal dendrites of the CA1 pyramidal cells (Fig. 11.8). The sizes and shapes of the spines and presynaptic profiles in this region are quite variable and may be related to the physiological efficacy of the synapses in CA1.

The associational projections from CA3 to CA3 are also organized in a highly systematic fashion and again terminate throughout stratum radiatum and oriens. One somewhat idiosyncratic facet of this projection is that cells located proximally in CA3 only communicate with other cells in the proximal portion of CA3 of the same and adjacent septotemporal levels. Associational projections arising from mid- and distal portions of CA3, however, project throughout much of the transverse extent of CA3 and also project much more extensively along the septotemporal axis.

An important feature of the CA3-to-CA3 associational and CA3-to-CA1 Schaffer collateral projections is that they are both divergently distributed along the septotemporal axis. Single CA3 and CA2 pyramidal cells give rise to highly arborized axonal plexuses that distribute to as much as 75% of the septotemporal extent of the ipsilateral and contralateral CA1 fields (Tamamaki et al., 1984, 1988). Using intracellular techniques, Li et al. (1994) have found that the total length of the axonal plexus from single CA3 neurons can be as long as 150–300 mm and that a single CA3 cell may contact as many as 30,000 to 60,000 neurons in the ipsilateral hippocampus!

In the rat, but not in the monkey (Amaral et al., 1984; Demeter et al., 1985), the CA3 pyramidal cells give rise to commissural projections to the CA3, CA2 and CA1 regions of the contralateral hippocampal formation (Swanson et al., 1978). The same CA3 cells give rise both to ipsilateral and commissural projections (Swanson et al., 1980). Although the commissural projections roughly follow the same topographic organization and generally terminate in homologous regions on both sides, there are minor differences in the distribution of terminals. If a projection is heavier to stratum oriens on the ipsilateral side, for example, it may be heavier in stratum radiatum on the contralateral side (Swanson et al., 1978). As with the commissural projections from the dentate gyrus, CA3 fibers to the contralateral hippocampus form asymmetric synapses on the spines of pyramidal cells in CA3 and CA1 (Gottlieb and Cowan, 1972) but also terminate on the smooth dendrites of interneurons (Frotscher and Zimmer, 1983).

Projections to Other Brain Regions. Until the mid 1970s, it was commonly assumed that the hippocampal fields (CA1–CA3) gave rise to all of the subcortical connections to the basal forebrain and diencephalon. But Swanson and Cowan (1975) demonstrated that most of these projections actually originate from the subiculum. The only sizable subcortical projection from CA3 is to the lateral septal nucleus (Swanson and Cowan, 1977). The CA3 projection to the septal complex is distinct from other hippocampal projections to the septal region in that it is bilateral. Some CA3 fibers cross in the ventral hippocampal commissure to innervate the homologous region of the contralateral lateral septal nucleus. Interestingly, essentially all of the CA3 cells give rise to projections both to CA1 and to the lateral septal nucleus (Swanson et al., 1980). It should

be noted that at least some of the hippocampal neurons that project to the septal region are GABAergic (Toth and Freund 1992).

The septal nucleus also provides the major subcortical input to CA3. As with the dentate gyrus, the septal projection originates mainly in the medial septal nucleus and nucleus of the diagonal band of Broca. The projection appears to terminate most heavily in stratum oriens and to a lesser extent in stratum radiatum (Nyakas et al., 1987; Gaykema et al., 1990). As in the dentate gyrus, the GABAergic component of the septal projection to the CA3 field terminates mainly on GABAergic interneurons (Freund and Antal, 1988; Gulyas et al., 1990).

The CA3 field also receives inputs from the noradrenergic nucleus locus coeruleus. Noradrenergic fibers and terminals are most densely distributed in the stratum lucidum and in the most superficial portion of stratum lacunosum-moleculare. A much thinner plexus of noradrenergic axons is distributed throughout the other layers of CA3. Serotonergic fibers are diffusely and sparsely distributed in CA3 and there are few, if any, dopaminergic fibers in this field (Swanson et al., 1987). As in the dentate gyrus, the serotonergic fibers, though diffusely distributed, nonetheless appear to terminate preferentially on interneurons (Freund et al., 1990) with axons that innervate the distal dendrites of pyramidal cells.

SYNAPTIC CONNECTIONS OF CA2

The CA2 field is relatively narrow and is located distal to the end of the mossy fiber projection; it is typically no wider than approximately 250 μm. It is made up of large, darkly staining pyramidal cells, like those of CA3. However, the CA2 pyramidal cells lack the thorny excrescences that are characteristic of CA3 pyramidal cells (Lorente de Nó, 1934; Tamamaki et al., 1988). A number of immunohistochemical studies have also demonstrated differential labeling of CA2. This region demonstrates denser acetylcholinesterase staining and much denser labeling for the calcium-binding protein parvalbumin than adjacent regions of CA3 or CA1 (Bainbridge and Miller, 1982). This is of interest since the calcium-binding proteins are considered to be protective of ischemic or excitotoxic cell death and the CA2 region is purported to be the "resistant sector" described in the human epilepsy literature (Corsellis and Bruton, 1983).

The intrahippocampal connections of CA2 resemble, in part, those of the distal portions of CA3, but there are also some distinguishing characteristics. Like CA3, the CA2 cells give rise to a projection to CA1 (Ishizuka et al., 1990). The projection is rather sparse and diffuse, however, and does not clearly follow the gradient rules established by the CA3 to CA1 projection. Interestingly, more collaterals from CA2 are distributed to the polymorphic layer of the dentate gyrus than from any portion of CA3.

There has been little work dealing specifically with the extrinsic inputs and outputs of CA2. In general, CA2 appears to share the connections of CA3. However, CA2 appears to receive a particularly prominent innervation from the supramammillary area (Haglund et al., 1984) and from the tuberomammillary nucleus (Köhler et al., 1985).

SYNAPTIC CONNECTIONS OF CA1

Unlike the CA3 field, pyramidal cells in CA1 do not appear to give rise to a major set of collaterals that distribute within CA1 (Amaral et al., 1991; Tamamaki et al., 1987), i.e. they have few associational connections. As the CA1 axons extend in the alveus or

in stratum oriens towards the subiculum, occasional collaterals do arise and appear to enter stratum oriens and the pyramidal cell layer. It is likely that these collaterals terminate on the basal dendrites of other CA1 cells (Deuchars and Thomson, 1996). What is clear, however, is that the massive associational network which is so apparent in CA3 is largely missing in CA1. Whereas it was thought that the CA1 field gave rise to no commissural connections (Swanson et al., 1978), it now appears that a small number of CA1 neurons may project to the contralateral CA1 (Van Groen and Wyss, 1990).

The CA1 field receives a similar but substantially lighter septal projection than CA3 (Nyakas et al., 1987). As with CA3, the CA1 field receives light noradrenergic and serotonergic projections. The distal portion of CA1 receives a fairly substantial input from the amygdaloid complex (Krettek and Price, 1977b). Fibers originating in the basolateral nucleus terminate in stratum lacunosum-moleculare of the CA1 field; this input from the amygdala appears to be restricted to the temporal third of CA1.

The thalamic inputs to the hippocampal formation have received relatively little attention. It has been known for some time that the anterior thalamic complex is intimately interconnected with the subiculum and the presubiculum. Herkenham (1978) demonstrated fairly prominent projections from midline (or nonspecific) regions of thalamus to several fields of the hippocampal formation. In particular, the small midline nucleus reuniens gives rise to a prominent projection to the stratum lacunosum-moleculare of CA1. Wouterlood and colleagues (1990; Dolleman-Van der Weel and Witter, 1992) found that the nucleus reuniens projections travel to the CA1 field via the internal capsule and cingulum bundle rather than through the fimbria/fornix. The nucleus reuniens projection terminates massively in stratum lacunosum-moleculare and innervates all septotemporal fields. Electronmicroscopic analysis indicates that the nucleus reuniens fibers terminate with asymmetric synapses on spines and thin dendritic shafts in stratum lacunosum-moleculare.

The CA1 field gives rise to two intrahippocampal projections. The first is a topographically organized projection to the adjacent subiculum (Amaral et al., 1991). The second is to the deep layers of the entorhinal cortex.

Axons of CA1 pyramidal cells descend into stratum oriens or the alveus and bend sharply towards the subiculum (Finch et al., 1983; Tamamaki et al., 1988; Amaral et al., 1991). The fibers re-enter the pyramidal cell layer of the subiculum and ramify profusely in the pyramidal cell layer and in the deep portion of the molecular layer. Unlike the CA3 to CA1 projection, which distributes throughout CA1 in a gradient fashion, the CA1 projection ends in a columnar fashion in the subiculum. CA1 cells located proximally in the field project to the distal third of the subiculum, whereas CA1 cells located distally in the field project just across the border into the proximal portion of the subiculum; the mid-portion of CA1 projects to the mid-portion of the subiculum (Amaral et al., 1991). Tamamaki et al. (1988) injected single CA1 pyramidal cells with horseradish peroxidase and demonstrated that individual axonal plexuses distribute to about one-third the width of the subicular pyramidal cell layer. Thus, the CA1 to subiculum projection segments these structures roughly into thirds.

CA1 is the first hippocampal field that originates a return projection to the entorhinal cortex and is thus different from the dentate gyrus and fields CA3/CA2 in this respect. Projections from CA1 to the entorhinal cortex originate from the full septotemporal and transverse extent of CA1 and appear to terminate most densely in the medial

entorhinal cortex, although projections also reach the lateral entorhinal cortex. The CA1 projections to the entorhinal cortex terminate predominantly in layer V (Swanson and Cowan, 1977; Finch and Babb, 1980, 1981; Van Groen and Wyss, 1990).

PHYSIOLOGICAL AND PHARMACOLOGICAL PROPERTIES

GENERAL PROPERTIES

Basic Response. As mentioned in previous sections, the highly structured and organized arrangement of synaptic pathways makes the hippocampus ideal for studying synaptic actions in vivo or in vitro (Andersen et al., 1971). Single-shock electrical stimulations to the perforant path, mossy fibers, or Schaffer collaterals result in a characteristic sequence of excitation followed by inhibition in the appropriate target neurons. The excitation typically precedes the inhibition by a few milliseconds but otherwise they overlap in time (Barrionuevo et al., 1986). The inhibition arises from the feedforward and feedback (recurrent) connections described above and often has two phases, a fast and a slow phase (see below). Some of the first recordings of synaptic actions in the hippocampus were made by Andersen and colleagues using electrical field recordings in vivo (see Langmoen and Andersen, 1981).

Extracellular Responses. Electrical field recordings represent the summed responses from a number of neurons in the vicinity of the recording electrode. Because of the orderly arrangement of pyramidal neurons and their dendrites, the electrical fields generated by active neurons have symmetry along the septal-temporal and cell-layer dimensions and asymmetry along the dendritic-somatic axis. This two-dimensional symmetry and one-dimensional assymetry makes electrical field recordings in hippocampus quite informative. For example, it can be shown that under appropriate conditions, the time course of the field potential is approximately equal to the time course of the underlying synaptic current (see Johnston and Wu, 1995). Furthermore, if multiple recordings are made at different sites along the dendritic axis, it is possible to localize the approximate site of generation of the electrical response using a technique called *current-source density analysis* (Haberly and Shepherd, 1973; Richardson et al., 1987).

Because current flows into the dendrites during excitatory synaptic activity, a field-recording electrode in stratum radiatum records first a brief negative-going transient that results from the volley of action potentials in the presynaptic fibers (called the *fiber volley*) followed by a slower negative-going potential with a time course similar to that of the underlying excitatory synaptic currents (refer to Fig. 11.9). This latter waveform is called a *population excitatory postsynaptic potential*, or *pEPSP*, to signify that the measured potential results from the summed activity across a population of neurons. The current flowing into the dendrites during this pEPSP will exit the neurons near the cell body layer so that a field electrode in *stratum pyramidale* will record a positive-going potential during this same synaptic event. If the intensity of the synaptic input is sufficient to evoke action potentials in the neurons, then the field electrode in *stratum pyramidale* will also record a negative-going potential (called a *pspike*) resulting from the inward current during the postsynaptic action potentials. Measurements of the initial slope of the pEPSP measured in either *stratum radiatum* or *stratum pyramidale* provide a reliable estimate of the intensity of synaptic activity, whereas

Long-term potentiation (see above) is considered to be the synaptic implementation of Hebb's postulate. A number of studies have shown that simultaneous presynaptic activity and postsynaptic depolarization are required for the induction of LTP (Kelso et al., 1986; Malinow and Miller, 1986; Wigstrom et al., 1986). Under physiological conditions the postsynaptic depolarization may be the back-propagating action potential (Magee and Johnston, 1997; Markram et al., 1997; see Fig. 11.17). It thus can provide the feedback signal from the axon to the synaptic input region than an output of the neuron has occurred. The signal may be the amplitude of the action potential that unblocks NMDA receptors or opens Ca^{2+} channels. Either way, an increase in $[Ca^{2+}]_i$ in the spine and dendrites occurs and leads to LTP of the active synapses. The amplitude of the back-propagating action potential is controlled by local IPSPs and EPSPs (Tsubokawa and Ross, 1996). IPSPs on specific dendritic branches will either reduce the amplitude of the action potential or prevent it from fully propagating into that dendrites. On the other hand, EPSPs will increase the amplitude of back-propagating action potentials and facilitate the propagation of the action potential into specific branches (Magee and Johnston, 1997; Hoffman et al., 1997). In this way, local EPSPs and IPSPs can control and guide the back-propagating action potential into different regions of the dendrites and thus control Hebbian learning. None of this would be possible without the active properties of dendrites.

FUNCTIONAL SYNTHESIS

LEARNING AND MEMORY

Perhaps the most widely accepted and long-lived proposal about hippocampal function relates to its role in memory (Eichenbaum, 1994). It has been known for nearly a century that damage to certain brain regions can result in an enduring amnesic syndrome that is characterized by a complete, or near complete, anterograde amnesia. Affected patients are incapable of recreating a record of day-to-day events. It is now clear that damage isolated to the human hippocampal formation is sufficient to produce this form of memory impairment. The most famous example of this is the patient with the initials H.M. As a young man, H.M. suffered from epilepsy that was so severe that it was life threatening. In 1953, H.M. underwent a neurosurgical procedure in which the hippocampal formation and surrounding brain tissue on both sides of his brain were removed. Although this surgery substantially reduced his seizures, there was a dramatic side effect. From the time of his surgery until the present day, H.M. has not been able to store any new information into long-term memory. In all other respects, however, H.M.'s cognitive functions appear normal. More recently, a number of other patients with bilateral damage confined to the hippocampus have been described. Patient R.B. was reported by Zola-Morgan and colleagues (1986). R.B. became ischemic following coronary bypass surgery and was neuropsychologically evaluated for 5 years after the incident. Like H.M., R.B. demonstrated a substantial anterograde memory impairment with little or no loss of memories formed before his surgery. R.B.'s brain was subjected to postmortem analysis and the only pathology that could be associated with his memory defect was a bilateral, complete loss of the CA1 field of the hippocampus. Since his amnesia was less severe than H.M.'s, it has been proposed that the severity of the memory impairment may depend on the amount of the hippocampal formation

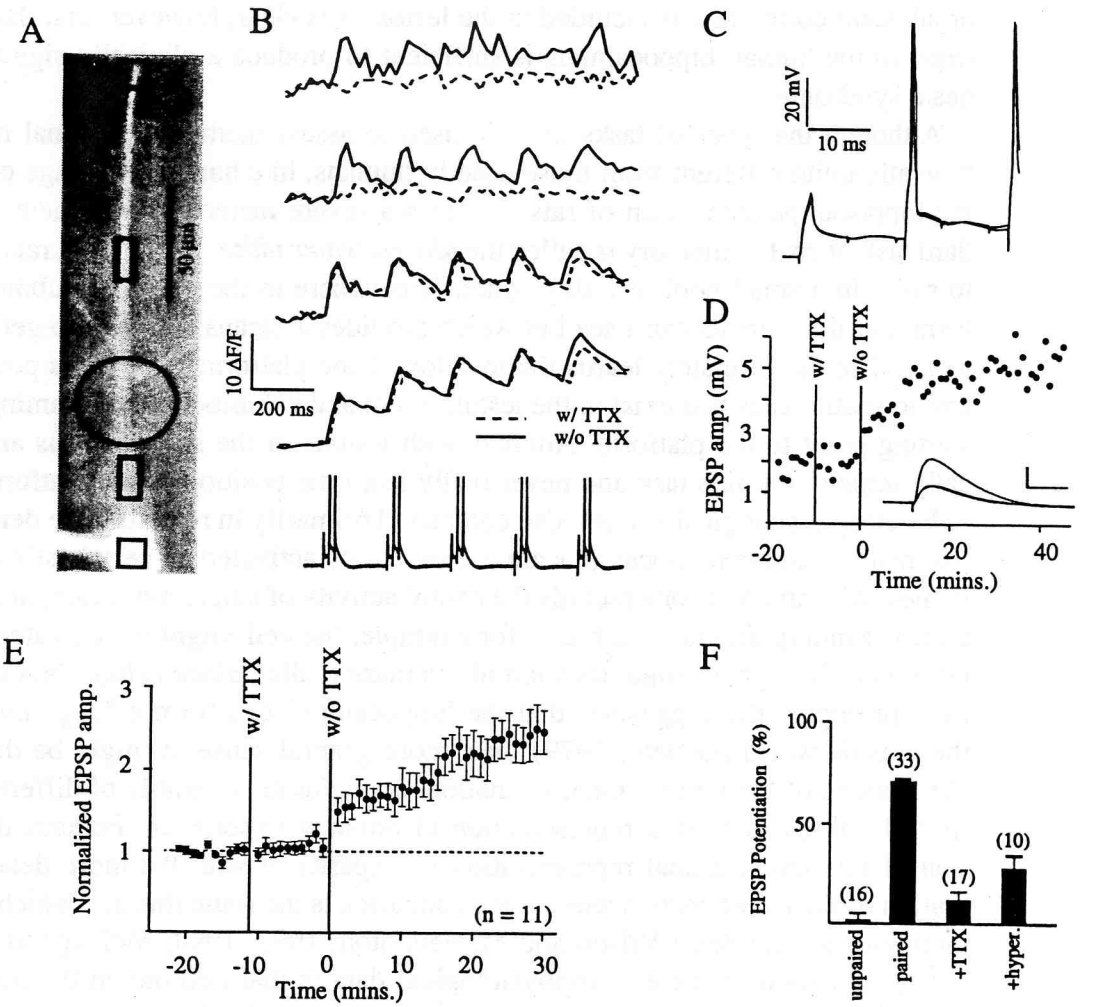

Fig. 11.17. Back-propagating action potentials paired with EPSPs induce LTP. **A:** Fura-filled CA1 pyramidal neuron with somatic electrode. Approximate area of TTX application shown by oval. **B:** Superimposed optical recordings of changes in fura-2 fluorescence from regions of the neuron delimited by the boxes in A. An increase in $[Ca^{2+}]_i$ is represented by an increase in $\Delta F/F$. Traces are from progressively more proximal regions moving down the column in B. Dashed lines are average $\Delta F/F$ during pairing protocol given along with a transient application of 10 μM TTX to dendrite. Solid lines are average $\Delta F/F$ during pairing protocol given without TTX application (approximately 11 min later). The rise in $[Ca^{2+}]_i$ is similar in regions of the neuron proximal to the TTX application and significantly reduced in those regions distal to TTX application site. Lower trace is somatic voltage during paired train. **C:** Expanded somatic voltage recordings during the first burst of paired stimuli for trains with the TTX application and without it. No appreciable differences are observable. First current injection was subthreshold in all traces, so only two action potentials were evoked during each individual burst. **D:** Plot of EPSP amplitude for the same neuron showing that paired stimuli without back-propagating action potentials do not modify EPSP amplitude, whereas subsequent paired stimuli with back propagating action potentials do result in a long-term, large magnitude increase in EPSP amplitude. Average EPSPs for last 2 min of each period shown in inset (control, +TTX, −TTX). **E:** Grouped data showing normalized EPSP amplitude after paired stimulation with and without TTX application. **F:** Summary of mean LTP amplitude under various experimental conditions. Plot shows the amount of EPSP potentiation, plotted as percent of control, for all cells under each condition. Potentiation was calculated by dividing the average EPSP amplitude at 10–15 min poststimulation by the average control EPSP amplitude. [From Magee and Johnston, 1997, with permission.]

or adjacent cortex that is included in the lesion. It is clear, however, that damage confined to the human hippocampus is sufficient to produce a clinically significant amnesic syndrome.

Although the types of tasks that are used to assess memory in animal models are typically quite different from those used in humans, like humans, damage confined to the hippocampal formation of rats produces a severe memory impairment. One standard task of spatial memory is called the *Morris water maze*. In this task, rats are placed to swim in a small pool of milky water. Somewhere in the pool is a submerged platform that the animals can't see but which provides a means for them to get out of the water. The rat ultimately learns the location of the platform through its position relative to spatial cues that exist in the testing room and exhibits rapid swimming from the starting point to the platform. Animals with lesions of the hippocampus are dramatically impaired in this task and never really learn the position of the platform.

Electrophysiological studies also conducted primarily in rodents have demonstrated that neurons in the hippocampus are preferentially activated by certain stimuli located in the environment. If one records the neural activity of single hippocampal cells while a rat is running around in a maze, for example, the cell might be activated when the rat travels through a certain location of the maze (called *place cells*). Data of this type have prompted the suggestion that the hippocampus can form a "cognitive map" of the outside world (Okeefe, 1979). In a more general sense, it might be thought that the neurons of the hippocampal formation, acting as an assembly of differentially activated units, can form a representation of ongoing experience. Perhaps the interaction of this hippocampal representation of experience with the more detailed information of the experience located in the neocortex is the route through which long-term memories are formed (Wilson and McNaughton, 1993, 1994; McHugh et al., 1996). One implication of the electrophysiological data is that neurons in the hippocampal formation are not uniquely sensitive to certain types of information. Rather, neurons in the hippocampal formation may act more like random-access memory (RAM) in a computer and are therefore potentially activated by all types of information. Since it would be difficult for evolution to anticipate all the various forms of information that might need to be stored as memory, a generalized memory buffer system would be highly adaptive.

The hippocampus displays very characteristic brain-wave activity that may be associated with learning and memory. When animals are exploring their environment, electroencephalographic (EEG) activity of 5–10 Hz frequencies (theta) are recorded (Okeefe, 1979; Buzsaki, 1989). When the animal stops exploring and is in a period of quiet wakefulness, the theta frequencies cease and are replaced by sharp-wave activity consisting of large amplitude, irregularly occurring waveforms. These two types of EEG patterns are mutually exclusive. One theory holds that during theta (exploratory) activity the hippocampus is acquiring a new representation of its environment while during sharp-wave (quiet) activity (and also during slow-wave sleep) the hippocampus is facilitating the consolidation of this information in the form of long-term memories elsewhere in the cortex (Buzsaki, 1989; Skaggs and McNaughton, 1996).

DISEASES OF THE HIPPOCAMPUS

The hippocampus has been implicated in a number of neurological and psychiatric disorders, including epilepsy, Alzheimer's disease, and schizophrenia. As mentioned at

the beginning of this chapter, the hippocampus has the lowest seizure threshold in the brain. In animal models of epilepsy, much of the electrical activity associated with seizures can be recorded from the hippocampus either in vivo or in vitro (Traub et al., 1989; see Fig. 11.18). The epileptiform activity so recorded is characterized by large, synchronous discharges that occur rhythmically and are often initiated in the CA2 or CA3 regions (Johnston and Brown, 1981, 1984, 1986). The propensity for the hippocampus to exhibit this epileptiform activity has been attributed to the recurrent excitatory connections among pyramidal neurons and the tendency for CA3 neurons to fire in bursts of action potentials. Under normal conditions the strong inhibition mediated by the various GABAergic interneurons described above prevents this abnormal activity from manifesting itself. Subtle changes in the firing properties of neurons or in the balance between excitation and inhibition, however, can permit a breakthrough of this hyperexcitable state leading to seizures.

An early and devastating feature of the onset of Alzheimer's disease is the inability to form new memories. Ultimately, even old memories weaken and fail. Because of the important role of the hippocampus in learning and memory, it is not surprising that the hippocampus is heavily damaged in Alzheimer's disease. In fact, it has been suggested that the hippocampus is functionally disconnected from the rest of the brain in this disease (Hyman et al., 1984). Moreover, there is suggestive evidence that the en-

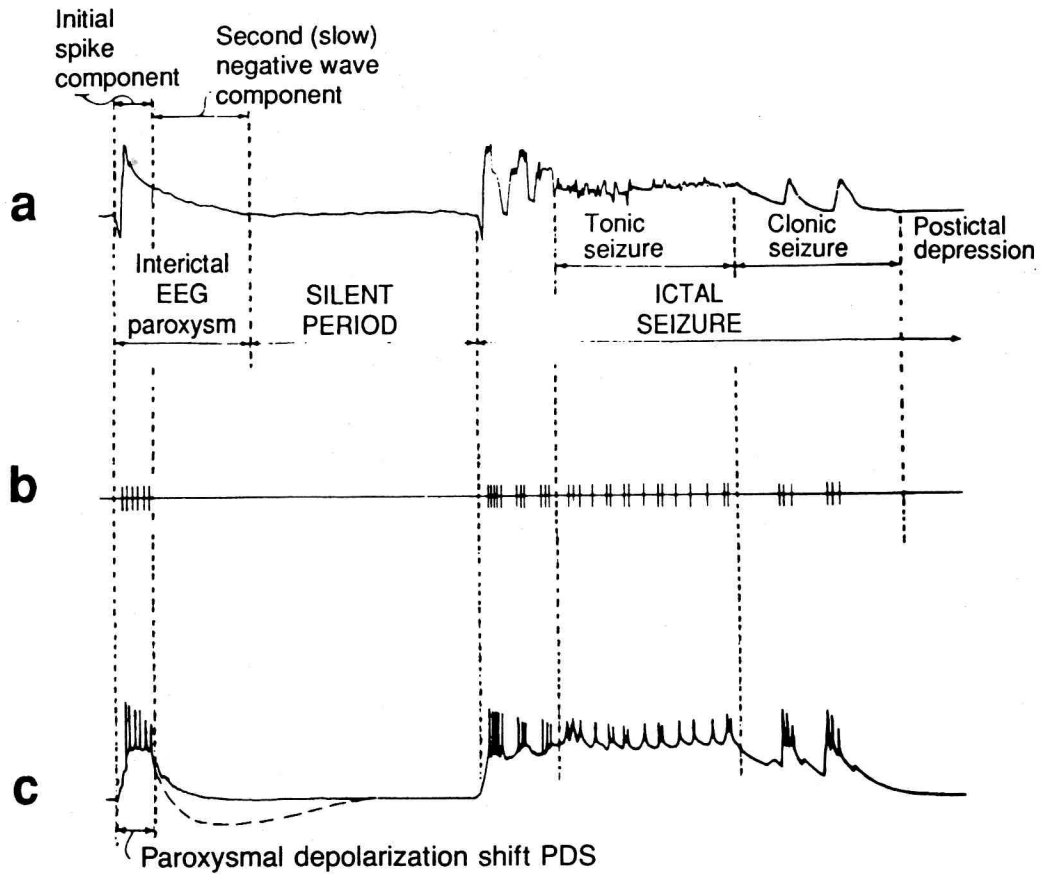

Fig. 11.18. Relationship between (a) cortical EEG and (b) extracellular and (c) intracellular discharges from a feline, penicillin-induced, spontaneous epileptiform discharge. [From Ayala et al., 1970, with permission.]

torhinal cortex may be one of the first brain regions in which Alzheimer's pathology becomes apparent. Although other parts of the brain are also affected, the ability of the hippocampus to process new information is seriously impaired in Alzheimer's disease. The hippocampus is also particularly vulnerable to ischemia and anoxia. In many patients who sustain these conditions, the hippocampus is one of only a few brain regions in which neuronal loss is observed. It appears that this loss is due to an excitotoxicity that may be mediated through the NMDA receptor. Some have proposed that the price the hippocampus pays for being able to rapidly encode new information is that it is inherently unstable and thus prone to a number of metabolic stressors. Finally, the link between schizophrenia and the hippocampus is not so clear. The principal finding is that the hippocampus is significantly smaller and has altered morphology in patients with schizophrenia (Luchins, 1990). Why these alterations should lead to the hallucinations and other altered mentation associated with schizophrenia is not known.