1 The hippocampus in context

Review of anatomy

In this chapter we shall review some aspects of the anatomy and physiology of the hippocampus, considering the hippocampus as only one component of the whole brain. We shall discuss also some clinical consequences of abnormal hippocampal function (epilepsy, amnestic states). Our purpose is to provide a biological background for the more detailed physiological and mathematical material to follow. We wish to define some of the relevant questions that can be answered in brain slices and in computer models of brain slices. We shall move freely between observations of the hippocampus from many different species (rodents, nonhuman primates, humans, and so on), assuming that the same general principles apply to all of them.

The hippocampus is a cortical structure that is necessary for the formation of new memories. The detailed mechanisms by which this function is accomplished are not well understood. The hippocampus in rodents contains cells that respond to spatial location ("place cells"). It generates characteristic EEG rhythms that depend on the behavioral state of animal. The hippocampus readily produces seizures in experimental contexts, and epileptic seizures originating in or near the hippocampus pose an important clinical problem.

The hippocampus forms a rather large part of the rodent brain (Paxinos and Watson, 1986). There is one hippocampus on each side of the brain. In humans, there is a hippocampus in each of the two medial temporal lobes. The hippocampus is anatomically the simplest type of cortex, with the cell bodies of the principal neurons aligned in a single layer. This fact is important to its usefulness in physiological experiments.

The “hippocampal formation” consists of the hippocampus proper together with other nearby structures: the dentate gyrus and the subiculum. The hippocampus proper is sometimes called the cornu Ammonis ("Ammon’s horn," abbreviated CA). Lorente de Nó (1934) defined subdivisions of the CA. The principal subdivisions are denoted CA1, CA2, and CA3. He used as criteria for his subdivisions the morphology
Neuronal networks of the hippocampus

Figure 1.1. Types of pyramidal cells in the rodent hippocampus (12-day-old mouse), stained by the Golgi method; “a” denotes the axon. Cell 12 shows a Schaffer collateral. Cell 7 is a pyramidal cell giving rise to longitudinal association fibers. Cell 19 is a pyramidal cell without a Schaffer collateral. Cell 9 is a pyramidal basket cell. Cells 21 and 22 are called “modified pyramids” by Lorente de Nó and lie in his region CA4. (From Lorente de Nó, 1934, with permission of the author.)

of the principal cell type (the pyramidal cells), the patterns of termination and distribution of fiber pathways (e.g., the mossy fibers), and the layout of the stratum pyramidale, the layer of cell bodies of the pyramidal cells (Figures 1.1 and 1.2). We shall follow the terminology of
The hippocampus in context

Lorente de Nó, with the proviso that the boundaries of CA2 are not always perfectly clear, and noting that CA1 and CA3 are in turn subdivided into subregions. CA1–3 pyramidal cells in the rodent lie in a well-defined visible band; this fact favors anatomical and physiological studies, as does the laminar pattern of the many fiber pathways: the mossy fibers, the Schaffer collaterals to the stratum radiatum of CA1, the commissural inputs to CA1 and CA3, the perforant path to the strata lacunosum and moleculare of CA1 to CA3 and to the dentate gyrus, and so on. Some estimates of the numbers of cells in human and rodent hippocampi are listed in Table 1.1.

In comparing the sizes of the human hippocampus and the rodent hippocampus, note that CA1 has increased relatively more than CA2–3. The human stratum pyramidale is relatively thicker, especially in CA1, with the band of cell bodies not as well defined as in rodents (Braak, 1974), and with CA1 somata reaching even to the alevus (Stephan, 1983).
4 Neuronal networks of the hippocampus

Table 1.1. Estimates of the numbers of pyramidal or granule cells in various hippocampal regions

<table>
<thead>
<tr>
<th>Species</th>
<th>Age</th>
<th>Region</th>
<th>Estimate</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>1 month</td>
<td>CA1</td>
<td>320,000–420,000</td>
<td>Boss et al., 1987</td>
</tr>
<tr>
<td>Rat</td>
<td>1 month</td>
<td>CA3</td>
<td>210,000–330,000</td>
<td>Boss et al., 1987</td>
</tr>
<tr>
<td>Rat</td>
<td>Adult</td>
<td>CA1–3</td>
<td>260,000</td>
<td>Cassell and Brown, 1977</td>
</tr>
<tr>
<td>Human</td>
<td>Adult</td>
<td>CA2–3</td>
<td>2,350,000</td>
<td>Brown and Cassell, 1980</td>
</tr>
<tr>
<td>Human</td>
<td>Adult</td>
<td>CA1</td>
<td>4,630,000</td>
<td>Zola-Morgan et al., 1986</td>
</tr>
<tr>
<td>Rat</td>
<td>1 month</td>
<td>Dentate</td>
<td>700,000–1,000,000</td>
<td>Boss et al., 1985</td>
</tr>
</tbody>
</table>

In order to put these cell numbers in context for the in vitro studies to be discussed later, we note that the number of cells in the rat CA3 region in vivo is about an order of magnitude larger than the number in the largest in vitro guinea pig preparation that we use. Thus, we estimate that the longitudinal CA3 slice (400 µ thick and 10 mm long) contains about 20,000 pyramidal cells. The CA3 region of a transverse slice may contain 3,000–5,000 cells.

The major cell type in the hippocampus proper is the pyramidal cell (Lorente de Nó, 1934), whereas in the dentate gyrus it is the dentate granule cell. Both of these groups of cells produce excitation in their postsynaptic cells that is fast (milliseconds). Significant minorities of inhibitory cells are recognized by their characteristic locations, morphologies, and axonal distributions; these include basket cells, chandelier cells (Somogyi et al., 1983b), mossy cells (Rihak, Seress, and Amaral, 1985), pyramidal basket cells (Rihak and Seress, 1983), and so on. Inhibitory cells can mediate either fast (lasting milliseconds to tens of milliseconds) or slow (tens to hundreds of milliseconds) types of inhibition. There have been studies that have related the electrical properties of inhibitory cells to their morphological types (Kawaguchi and Hama, 1987, 1988; Lacaille and Schwartzkroin, 1988a,b; Lacaille et al., 1987; Scharffman and Schwartzkroin, 1988b; Schwartzkroin and Kunkel, 1985; Schwartzkroin and Mathers, 1978). Most, but not all, of the nonpyramidal cells are presumed to be inhibitory. This conclusion is based on staining for the inhibitory neurotransmitter γ-aminobutyric acid (GABA) or the GABA-synthesizing enzyme glutamic acid decarboxylase (GAD) (Sloviter and Nilaver, 1987; Somogyi et al., 1983c). In some cases, dual intracellular recording has proved that certain cells are inhibitory (Knowles and Schwartzkroin, 1981a,b; Lacaille and Schwartzkroin, 1988a,b; Lacaille et al., 1987; Miles and Wong, 1984). Most of the long-range intra-
hippocampal connections, as well as hippocampal inputs and outputs, are excitatory, but there are exceptions. The exceptions include GABA-ergic fibers into the hippocampus that originate in the septum (Freund and Antal, 1988), as well as dentate hilar cells with commissural projections (Ribak et al., 1986).

Some of the major pathways within and involving the hippocampus are these: (i) the **perforant path**, originating in entorhinal cortex (EC); (ii) the **mossy fibers**, suprapyramidal and infrapyramidal, connecting dentate granule cells to CA3 pyramidal cells and hilar neurons (Claiborne, Amaral, and Cowan, 1986; Lorente de Nó, 1934; Yamamoto, 1982); (iii) the **Schaffer collaterals** of CA3 pyramidal axons, making en passant synapses onto CA1 pyramidal cells; (iv) the **commissural connections**; (v) the **recurrent excitatory connections** between CA3 pyramidal cells (MacVicar and Dudek, 1980a; Miles and Wong, 1986) and between CA1 pyramidal cells (Christian and Dudek, 1988b; Dichter, Herman, and Selzer, 1973; Hablitz, 1984); (vi) **inhibitory circuitry**, with inhibitory cells excited either by local pyramidal-cell collaterals or by afferent fibers or both (Alger and Nicoll, 1982a; Anderson, Eccles, and Loyning, 1963; Kehl and McLennan, 1985a,b; Newberry and Nicoll, 1984). The excitatory neurotransmitter used by the perforant-path input to the hippocampus is thought to be glutamate or a related amino acid (White et al., 1977b). The transmitter used by excitatory pathways within the hippocampus is also likely to be an excitatory amino acid (Crunelli, Forda, and Kelly, 1983; Nadler et al., 1976).

The so-called trisynaptic circuit consists of the following excitatory loop: entorhinal cortex to dentate granule cells via the perforant path, granule cells to CA3 pyramidal cells via the mossy fibers, and CA3 pyramidal cells to CA1 pyramidal cells via the Schaffer collaterals. Because CA1 cells project back to the entorhinal cortex via the subiculum, perhaps one should refer to the “tetrasynaptic circuit” or “pentasympathetic circuit.” The notion of the trisynaptic circuit is an oversimplification. It omits, for example, collateral connections between CA3 cells, the connections between granule cells that are presumed to be mediated via mossy cells in the hilus, perforant-path synapses onto CA1 and CA3 pyramidal cells, and both feedback and feedforward inhibition.

Some of these hippocampal pathways show clear spatial organization. This is particularly true of the mossy fibers, which tend to stay confined to transverse hippocampal “laminae” (Claiborne et al., 1986). The perforant path is also spatially structured: The lateromedial gradient along layers 2 and 3 of the EC is mapped onto the longitudinal gradient along the hippocampus (Witter and Groenewegen, 1984). In addition, layer 2 of the EC projects to the dentate and CA3, and layer 3 projects to CA1 (Steward and Scoville, 1976). Both CA3 pyramidal and hilar cells contribute to the commissural pathways, but apparently CA1 cells...
Neuronal networks of the hippocampus

do not (Gottlieb and Cowan, 1973). Schaffer-collateral synapses lie in the stratum radiatum of CA1, and commissural fibers from the contralateral CA3 region synapse in the stratum oriens and stratum radiatum of CA1 (Buzsáki and Eidelberg, 1982; Laurberg, 1979) as well as in CA3.

The inputs to the hippocampus can be divided into those from cortical structures (including the opposite hippocampus, the same hippocampus via associational fibers, the dentate gyrus, and the entorhinal cortex) and those from noncortical structures (including the septum/diagonal band, the hypothalamus, the brain-stem raphe nuclei, and the locus ceruleus). The outputs from the hippocampus can also be divided into those proceeding to cortical areas [the hippocampi themselves, the subiculum and entorhinal cortex, the medial frontal cortex, and the cingulate gyrus (Brodal, 1981)] and those proceeding to noncortical areas such as the septum. Most, but not all, of the output is carried via axons of pyramidal cells (Alonso and Köhler, 1982; Chronister and DeFrance, 1979; Finch, Nowlin, and Babb, 1983; Swanson and Cowan, 1977). The projection to the septum originates in both pyramidal and nonpyramidal cells (Alonso and Köhler, 1982). The fimbria/ fornix was once considered a major output pathway from the hippocampus to the septum and hypothalamus, but it is now known that most of the fibers in the fimbria/fornix originate from cells in the subiculum rather than the hippocampus proper (Chronister, Sikes, and White, 1976; Meibach and Siegel, 1977a).

It may be possible to make a functional distinction between cortical and subcortical inputs to the hippocampus. The cortical inputs seem likely to carry detailed, time-dependent information driven by external events. In contrast, subcortical inputs serve a modulatory function by permitting or enabling different oscillatory modes of the hippocampal circuitry. This would be analogous to the way that modulators can cause invertebrate central pattern generators to switch between different oscillatory modes (Getting and Dekin, 1985a,b; Heinzl, 1988a,b; Heinzl and Selverston, 1988). This hypothesis regarding the differences between cortical and subcortical inputs is suggested by the differing time courses of the respective neurotransmitters (rapid for cortical inputs, slower for at least some of the subcortical inputs), as well as by the numbers of cells supplying the inputs (large for cortical sources, smaller for subcortical sources, particularly from the locus ceruleus). These distinctions, however, are not absolute, because cortical inputs may co-release peptides along with the usual amino acid transmitter, whereas the subcortical septal inputs include the rapidly acting GABA in addition to the slower-acting acetylcholine.

Let us now consider the nonhippocampal inputs and outputs of the cortical areas that impinge on the hippocampus – the subicular complex and entorhinal cortex – together with some of the interconnections of
The hippocampus in context

these respective regions. The dorsolateral prefrontal cortex sends inputs to the presubiculum or parasubiculum, depending on the species; the subiculum in turn projects to the ventral prefrontal cortex (Cavado and Reinoso-Suárez, 1988). The subiculum also projects to the hypothalamus, septum, anterior thalamus, cingulate cortex, and entorhinal cortex (Brodal, 1981), as well as the medial frontal cortex, parahippocampal region, amygdala, nucleus accumbens, and lateral dorsal thalamic nuclei (Rosen and Van Hoesen, 1977). There are inputs to the entorhinal cortex from the orbitofrontal cortex, temporal pole, perihinal cortex, superior temporal gyrus, parahippocampal gyrus, and retrosplenial cortex (Insauti and Amaral, 1988). Brodal (1981) lists as inputs to the EC the following: olfactory bulb, prepyriform and periamygdaloid cortex, amygdala, medial septum, dorsal raphe nucleus, locus ceruleus, the CA3 region of the hippocampus, and parts of the thalamus. Most of the output from the EC is sent to the hippocampus, via the lateral and medial perforant paths. Seltzer and Pandya (1976), in studies of the rhesus monkey, found that the rostromedial temporal lobe, peristriate cortex, and caudal inferior parietal lobule (association areas for hearing, vision, and touch, respectively) projected to regions of the parahippocampal gyrus that in turn are known to project to the EC. The existence of these pathways implies that the EC receives multimodal “highly processed” information from several cortical regions (Lopes da Silva et al., 1985). In addition to exciting the hippocampus, the EC sends fibers to the septum (Crutcher, Madison, and Davis, 1981), as does the hippocampus, as discussed later. The subiculum receives inputs from CA1, the EC, and “virtually all areas along the base of the temporal lobe” (Van Hoesen, Rosene, and Mesulam, 1979). It projects back to many of these same regions (Berger et al., 1980; Finch et al., 1986; Rosene and Van Hoesen, 1977).

The cingulate cortex is another part of the “limbic system.” In addition to receiving afferents from the hippocampus, the cingulate is also excited by the anterior thalamus, subiculum, lateral septum, and areas of parietal, temporal, and prefrontal cortex (Brodal, 1981). The cingular likewise projects to the hippocampus, but also to the amygdala, septum, thalamus, prefrontal cortex, parietal association cortex, superior colliculus, pretectal area, periaqueductal gray, midbrain tegmen-
tum, and locus ceruleus (Brodal, 1981). (The reader will have noticed how the same regions are multiply interconnected with one another.)

We shall now briefly consider the subcortical inputs to the hippocampus. Many, perhaps all, of the transmitters released by these inputs act via intracellular second messengers (Nicoll, 1988). Most fibers from the septum release acetylcholine, whereas others release GABA; substance P is another possible transmitter (Vincent and McGeer, 1981). Acetylcholine has a number of actions, most of which have a slow onset and long
Neuronal networks of the hippocampus

duration (minutes). It decreases transmitter release from both excitatory and inhibitory presynaptic terminals (Haas, 1982; Segal, 1982, 1983, 1985; Valentino and Dingledine, 1981), blocks a slow calcium-dependent potassium conductance, $h_{K(Ca)}$ (Benardo and Prince, 1982; Cole and Nicoll, 1984), and blocks a voltage-dependent potassium current called the M current (Halliwell and Adams, 1982), with possible cellular depolarization and an increase in input resistance. Acetylcholine also seems to excite inhibitory cells (McCormick and Prince, 1985, 1986; Reese and Schwartzkroin, 1988; Strowbridge and Shepherd, 1988). The effects of acetylcholine have a latency of onset of tens of milliseconds to minutes and tend to last for minutes. Most of the GABA fibers from the septum appear to synapse onto inhibitory cells in the hippocampus (Freund and Antal, 1988); it is not known if GABA$_A$ or GABA$_B$ receptors are involved (Alger and Nicoll, 1982b). The latter case would be interesting, because the effects of activation of GABA$_A$ receptors are mediated by a second messenger and tend to be relatively long-lasting (Andrade, Malenka, and Nicoll, 1988). Further details of the septum-to-hippocampus pathway will be discussed later in the section on theta rhythm.

The locus ceruleus of the pons uses norepinephrine as transmitter. This compound decreases $h_{K(Ca)}$ and also hyperpolarizes pyramidal cells (Madsen and Nicoll, 1982, 1986a,b). The raphe nuclei use serotonin, a transmitter that hyperpolarizes many CA1 cells (Andrade et al., 1986; Segal, 1980), and may directly excite inhibitory neurons (Guy and Ropert, 1990). Occasionally, serotonin depolarizes CA1 cells in association with a decreased input resistance (Jahnson, 1980). Variable effects of serotonin may derive from the existence of multiple receptor types, which may lead to activation of one potassium conductance while others are suppressed (Andrade and Nicoll, 1987; Colino and Halliwell, 1987). Some serotonin receptors are coupled via a second messenger to the same potassium channels that are activated by GABA$_A$ receptors (Andrade et al., 1986). Cells in the mesencephalic reticular formation release histamine into the hippocampus (Garbarg et al., 1974). Peptides that are found in the hippocampus or that exert effects on hippocampal neurons include cholecystokinin (CCK), vasoactive intestinal peptide (VIP), substance P, neotensin, met-enkephalin, leu-enkephalin (Tielen, van Leeuwen, and Lopes da Silva, 1982), vasopressin (Mühlthaler, Dreifuss, and Gähwiler, 1982), and somatostatin (Roberts et al., 1984). The latter compound may act presynaptically to diminish GABA release (Scharfman and Schwartzkroin, 1988a). Similarly, neuropeptide Y (NPY) is a peptide transmitter found in the hippocampus that appears to diminish, by a presynaptic mechanism, the action-potential-evoked release of excitatory transmitter (Colmers, Lukowiak, and Pittman, 1987). The cells of origin for NPY are not known with certainty; they may be intrinsic to the hippocampus, perhaps with NPY co-released with another transmitter.
The hippocampus in context

Having reviewed some of the anatomical organization of the hippocampus, we shall devote the remainder of this introductory chapter to four manifestations, normal and pathological, that have been associated with the hippocampus: memory disorders, spatial performance, certain types of EEG findings, and epilepsy.

Amnestic syndromes and the hippocampus

We shall now consider some behavioral syndromes wherein there is either definite or suggestive evidence of hippocampal dysfunction. In general, these clinical and experimental observations suggest that the hippocampus is essential for conceptual or declarative (Squire, Shimamura, and Amaral, 1989) memory (particularly for memory of events to which one is exposed only once), but not for procedural memory (the kind of memory involved in learning a skill with practice) (Squire, 1986).

A remarkable clinical syndrome called transient global amnesia was vividly described by Fisher and Adams (1964); see also Shuping, Rolfinson, and Toole (1980a). In this syndrome, there is a sudden onset of altered behavior, but with preservation of consciousness and personal identity. The patient appears bewildered and repeats certain questions over and over. He or she is not able to record new information for more than a few minutes. This state persists for some hours, and there is permanent amnesia for the period of involvement; but the patient can record new memories once the transient amnesic period is over (Kritchovsky, Squire, and Zouzounis, 1988). There is some suggestive evidence that this syndrome involves the hippocampus. For example, it has been reported in association with a glioma in the left (dominant) hippocampus (Shuping, Toole, and Alexander, 1980b), but it has also been reported with a thalamic lesion (Goldenberg, Wimmer, and Maly, 1983). The underlying pathogenesis is not known. One interesting hypothesis is that the hippocampus becomes transiently nonfunctional because of spreading depression (Olesen and Jurgensen, 1986), a phenomenon to which this brain region is known to be susceptible in vitro (Snow, Taylor, and Dudek, 1983). In this regard, transient global amnesia has been triggered by mild trauma (Haas and Ross, 1986), a procedure that can initiate spreading depression in the hippocampal slice. Complex partial seizure activity in the hippocampus also disrupts the registration of ongoing events, as described later (Halgren and Wilson, 1985). It is interesting that transient global amnesia can be triggered by orgasm (Mayeux, 1979). During orgasm there is intense electrical activity in the septum (Heath, 1972) that presumably would strongly drive the hippocampus.

Surgical lesions of the hippocampus bilaterally, in humans and in subhuman primates, also produce an amnestic syndrome in which "single-exposure" memory is particularly involved (Squire, 1986). In
Neuronal networks of the hippocampus

humans, the temporal stem, an area of subcortical white matter in the temporal lobe, was thought to represent a critical region for memory (Horel, 1978), but this idea has not been confirmed by primate experiments (Zola-Morgan, Squire, and Amaral, 1989a,b). The work with lesions dates back to the nineteenth century (Brown and Schäfer, 1888), but is now identified particularly with the Klüver-Bucy syndrome, seen in monkeys after a bilateral surgical lesion of the medial temporal region (including amygdala and hippocampus) (Klüver, 1951). The lesion also leads to secondary degenerative changes elsewhere, including changes in the anterior commissure, frontotemporal white matter, and connections to the cingulate cortex (Klüver, 1951). It may be relevant that the amygdala and hippocampus are interconnected structures; specifically, in primates, the amygdala projects to CA1, the subiculum, and to entorhinal cortex (Amaral, 1986). The operated animals show a failure of visual recognition and lose their fear of creatures that would normally frighten them (snakes, for example). They are compulsively hypersexual; they will put everything graspable into their mouths. Two recent abstracts suggest that in a temporal-lobe lesion of this sort, the amygdala lesion contributes to the “emotional” component, while damage to the perirhinal, parahippocampal, and perhaps hippocampal areas contributes to the memory deficit (Alvarez-Royo et al., 1988; Zola-Morgan, Squire, and Amaral 1988).

Further insight into the role of the hippocampus in memory has come from clinical observations of patients with more restricted lesions, as well as from animal experiments with controlled lesions. Thus, the famous patient HM had more restricted bilateral amygdala/hippocampal lesions produced in a neurosurgical procedure aimed at relieving his severe epileptic seizure disorder (Scoville and Milner, 1957). Postoperatively, he had severe anterograde amnesia (inability to form new memories) that has persisted; there was loss of some memories from a few years prior to surgery. HM remains unable to learn the meanings of new words (Gabrieli, Cohen, and Corkin, 1988).

Patients who recover from anoxic encephalopathy, such as that following cardiac arrest, may well have dementia, including a severe disorder of memory. The underlying neuropathology may be diffuse in these cases, however. One patient had dementia with more limited pathology: bilateral lesions involving CA1, the subiculum, and the amygdala (Volpe and Petito, 1985). Of particular interest is a patient with an amnestic syndrome in whom the lesion was confined to the hippocampi: There was bilateral destruction of CA1 (Zola-Morgan, Squire, and Amaral, 1986) (Figure 1.3). In this patient, immediate memory was relatively preserved, but material to be recalled was irrevocably lost over some minutes.

Patient HM was more amnesic than was the patient of Zola-Morgan et