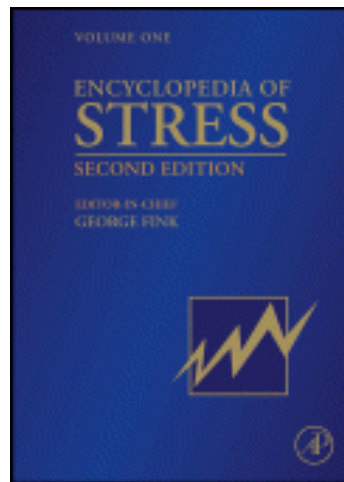


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Hippocampal Neurons

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Glossary

- Adenylyl cyclase* A protein enzyme that when activated, for example by a G-protein, catalyzes the formation of an intracellular second-messenger molecule, cyclic adenosine monophosphate (cAMP).
- Cation channel* A protein complex embedded in a cell's membrane that allows positively charged ions (e.g., Na⁺, K⁺, or Ca²⁺) to pass through the membrane.
- G-proteins* Guanine nucleotide (guanosine triphosphate, GTP, and guanosine diphosphate, GDP) binding proteins that associate with the intracellular portion of metabotropic receptors. G-protein alterations are the first step in a cascade of intracellular molecular changes triggered by neurotransmitter or hormone (ligand)

binding of metabotropic receptors at the membrane surface.

Neuropil

Brain region that consists primarily of neuronal processes (dendrites and axons) rather than neuronal cell bodies.

Spatial learning

Learning tasks in which optimal performance requires that the organism has learned the relative spatial relationship between objects in the environment. Spatial learning can be demonstrated by tasks in which the organism is able to select the most direct route to a location that it has been to before or, alternatively, by tasks in which the organism avoids revisiting places that it has been to before.

Overview

The hippocampal formation consists of the hippocampus and the closely associated dentate gyrus and subiculum. The hippocampal formation first attracted attention as a primitive region of the cortex that had an architecturally simple and orderly cellular organization. Strikingly detailed drawings of the microscopic organization of the hippocampal formation were provided by Ramón y Cajal in the late 1800s (Figure 1). This structure is dominated by the orderly alignment of two principal neuronal cell types: pyramidal cells and granule cells. Moreover, the principal cells of the hippocampal formation were found to be interconnected in such a way as to produce a simple intrinsic neurocircuit (the trisynaptic circuit). Interest in the hippocampal formation intensified when, based on human amnesic cases, it was found to be essential for the formation of new episodic memories and the acquisition of declarative facts. The intense study of the hippocampus has yielded the first characterized cellular functional response (long-term potentiation) believed to reflect the fundamental neuroplasticity underlying memory formation.

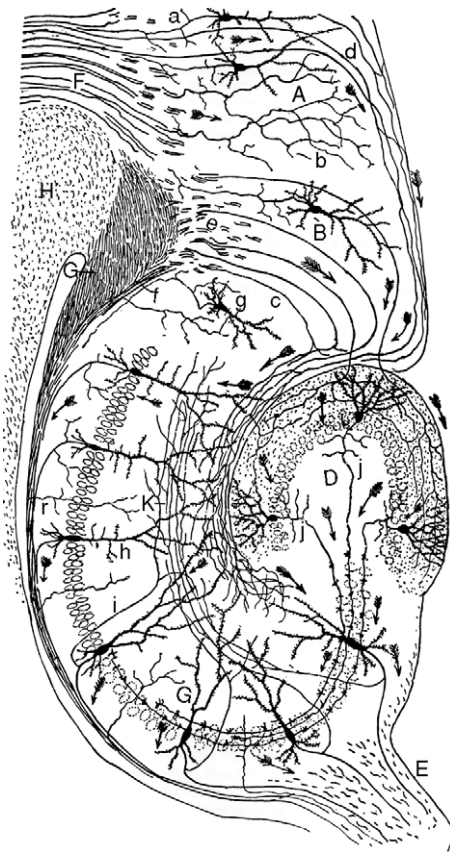


Figure 1 Drawing of a transverse section of the hippocampal formation highlighting the principal cells (e.g. B, D, G, h), their interconnections and presumed flow of neural impulses (arrows). Drawing by S. Ramón y Cajal, first published in 1911 (Ramón Y Cajal, *Histologie du système nerveux de l'Homme et des Vertébrés*. Paris: A. Maloine, 1911).

Subsequent study of the hippocampus has revealed a range of neuroplasticity phenomena that include dynamic changes in neuronal arborization, spine density, and synapse formation. Investigations in recent years have determined that neurogenesis is a routine feature of the adult dentate gyrus portion of the hippocampal formation. The characterization of these forms of hippocampal neuroplasticity has revolutionized recent neuroscience with the discovery that these neuroplastic changes are not restricted to critical developmental periods or recovery from brain injury but are a normal daily occurrence that persists throughout the life span.

Hippocampal Formation

Each of the components of the hippocampal formation is characterized by a single principal cell body layer sandwiched between two zones of neuropil, yielding a simplified version of cortex with only

three distinct layers. Extensively associated with the hippocampal formation, in terms of interconnections, is the adjacent six-layer entorhinal cortex. The hippocampus and its interleaved partner, the dentate gyrus, are two phylogenetically primitive cortical structures that are buried underneath the cortical mantle. In the human brain, these two enfolded sheets of rudimentary cortex are located within the temporal lobe (Figure 2). In the rodent brain, these structures extend more dorsal-anteriorly. The dorsal portion of the hippocampus is located immediately beneath the corpus callosum and has an anterior extension that approaches the septal region (Figure 3). The most caudal extent of the hippocampus is located in the ventral half of the caudal portion of rodent forebrain.

Dissected out of a rat brain, the combined dentate gyrus and hippocampus are somewhat banana-shaped. The longitudinal axis of this structure is often referred to as the septal-temporal axis of the hippocampus and dentate gyrus. The rostral approximately two-thirds of this structure is known as the dorsal hippocampus, and the caudal third is known as the ventral hippocampus. This structure is usually studied and depicted in the transverse/cross-sectional plane (Figure 3). The cellular organization of the hippocampus and dentate gyrus in mammals is remarkably consistent throughout its longitudinal extent. Recent anatomical studies, however, have demonstrated important differences in intrinsic and extrinsic connections within the dorsal and ventral hippocampus. These differences may have important functional significance. For example, there is some evidence that the dorsal hippocampus is more important for spatial learning and memory and that the ventral hippocampus selectively contributes to fear and other emotion-dependent behaviors and learning.

Laminar Organization of Dentate Gyrus and Hippocampus

The principal cell body layer of the hippocampal formation consists primarily of pyramidal cell bodies (hippocampus and subiculum) or granule cell bodies (dentate gyrus). The surrounding neuropil zones primarily comprise the proximal principal cells' dendrites and axons and the nerve terminals of extrinsic and intrinsic afferents. This laminar organization can be easily visualized when examining microscopically a transverse section of dentate gyrus and hippocampus (Figure 4a). Anatomists have subdivided the neuropil zones into different strata, based primarily on microscopic differences in the principal cell processes and the afferents and efferents present within each strata (Figure 4b). Note that each of these cortical

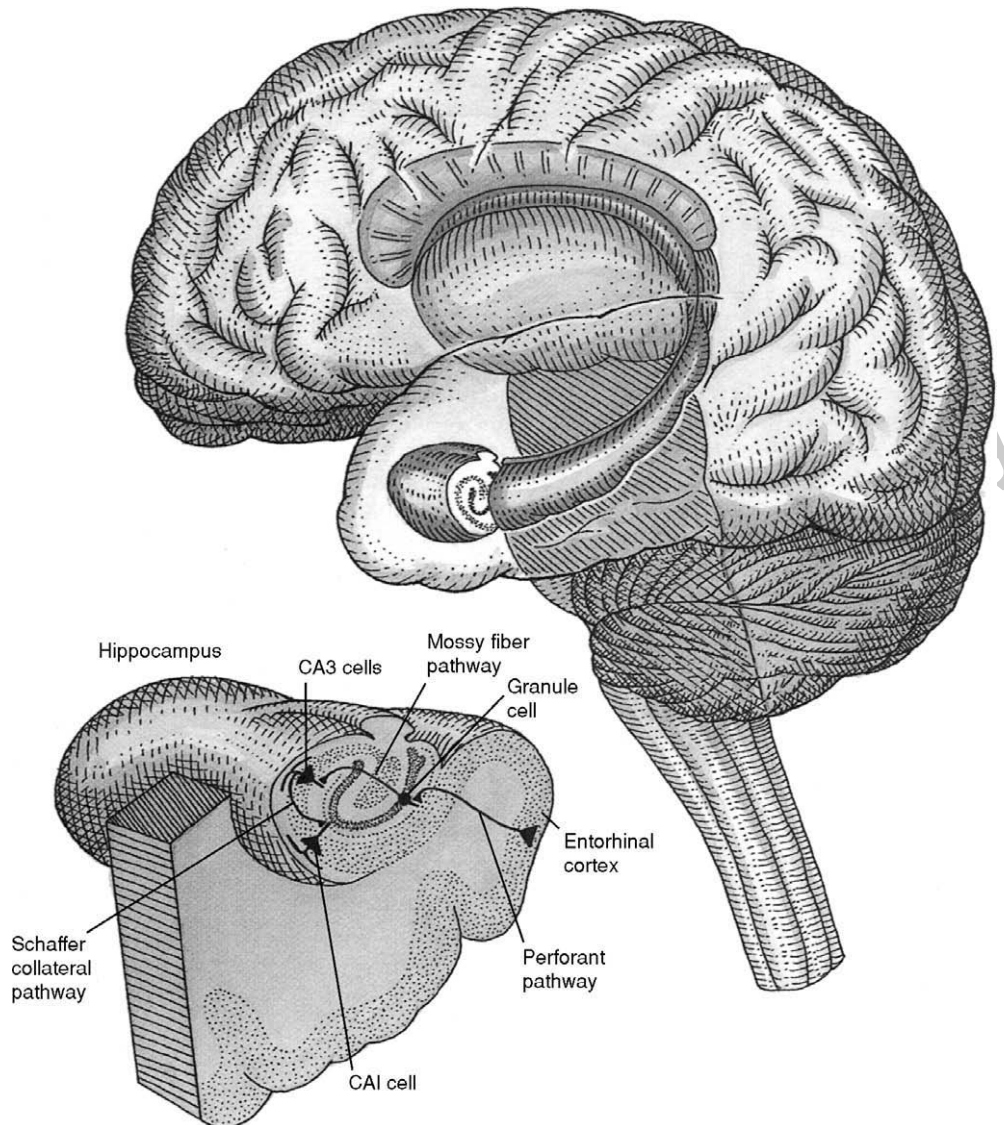


Figure 2 Relative location of hippocampal formation in human brain. The hippocampus and its interleaved partner, the dentate gyrus, reside beneath the cortical surface in the temporal lobe. An enlarged transverse slice of the hippocampus and dentate gyrus is depicted in the lower left portion of the figure. From Squire, L. R. and Kandel, E. R. (2000), *Memory, from mind to molecules*, New York: Scientific American Library.

sheet has been folded in half along its longitudinal axis. Therefore, when we view a cross section of this structure in the rat brain, the orderly aligned principal cell bodies form a C-shaped (hippocampus) or V-shaped (dentate gyrus) formation. As is evident when we view a horizontal cross section of ventral hippocampus, one edge of the hippocampal sheet is adjacent to the subiculum and entorhinal cortex (Figure 4c–d). The other edge of the hippocampal sheet is tucked inside the two folds of the dentate gyrus. The C-shaped formation of pyramidal cell bodies in the hippocampus is subdivided into three subfields based on morphological and interconnection distinctions. These subfields are designated

CA1, CA2, and CA3 (drawing on the Latin name for the hippocampus, *cornus Ammonius*, Ammon's horn). The CA3 region is adjacent to the dentate gyrus, and the CA1 region is adjacent to the subiculum. The smaller CA2 region has morphological, phenotypical, and connective features that overlap with those of the CA3 and CA1 subregions, but in combination makes for a clearly distinct functional zone of cells. The granule cells in the dentate gyrus are relatively uniform throughout the V-shaped formation in terms of morphology, innervation, and projections. The two folds of dentate gyrus giving rise to the V-shaped formation are commonly referred to as the enclosed and free blades, or the

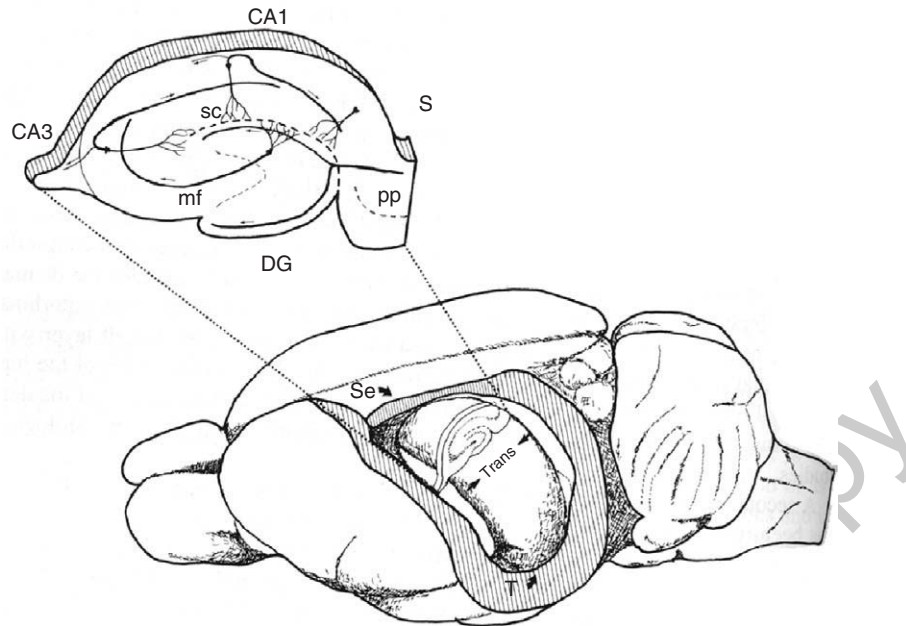


Figure 3 Relative location of hippocampal formation in rat brain. The hippocampus (including CA1 and CA3 subregions) and dentate gyrus (DG) form a banana-like structure with one end of the longitudinal axis located dorsal-rostrally near the septal (Se) region and the other end located ventral-caudally near the temporal (T) pole of the rat forebrain. An enlarged transverse slice is depicted in the upper portion of the figure. mf, mossy fiber; pp, perforant path; sc, Schaffer collateral; S, subiculum. From Amaral, D.G. and Witter, M.P. (1989) The three-dimensional organization of the hippocampal formation: a review of the anatomical data. *Neuroscience* 31, 571–591.

suprpyramidal and infrapyramidal blades, of the dentate gyrus. Recent studies indicate that there are some clear differences in the relative afferent connections to the two blades of the dentate gyrus as well as discriminable tendencies in their projection to CA3 subregions. The intervening space between the two granule cell body-forming blades of the dentate gyrus is known as the hilus or polymorphic region of the dentate gyrus.

Lammelar Organization (Trisynaptic Circuit) of Dentate Gyrus and Hippocampus

Significantly, many of the intrahippocampal neural connections are maintained within a narrow cross-sectional area (lammellae). A simple unidirectional trisynaptic connection among the components of the hippocampal formation was deduced by Ramón y Cajal based on microscopic architecture (Figure 1). Around 1970, Andersen and colleagues provided electrophysiological evidence to support a predominantly lammelar organization of hippocampal function. This trisynaptic circuit (Figure 5a) begins with pyramidal neurons predominantly localized in layer II of entorhinal cortex. These cells project (perforant pathway) to both blades of the dentate gyrus

and form synapses on granule neuron dendrites (synapse 1). The granule neurons project (mossy fiber pathway) to CA3 and form synapses on the apical dendrite of CA3 pyramidal neurons within the stratum lucidum (synapse 2). A collateral axonal branch of the CA3 pyramidal neurons projects (Schaffer collateral) to CA1 and forms synapses on basilar and apical dendrites of CA1 pyramidal neurons (synapse 3). The primary output from this circuit, and from the hippocampus overall, proceeds from CA1 neurons to the adjacent subiculum and entorhinal cortex as well as to subcortical structures.

More recent investigations have determined that there is considerable divergence and convergence within the longitudinal plane of connections between the entorhinal cortex and the dentate gyrus and between CA3 pyramidal neurons and other CA3 and CA1 cells. Only the mossy fiber connections between the dentate gyrus and CA3 are predominantly restricted to a cross-sectional lammellae. Nevertheless, a fairly thin cross section of the dentate gyrus and hippocampus contains a number of intact cells of each trisynaptic circuit component. Therefore, the hippocampal formation is ideally suited for *ex vivo* study, in which a 250- to 500- μm cross-section of this structure contains an electrophysiologically functional trisynaptic circuit. Consequently, with appropriate bath conditions for

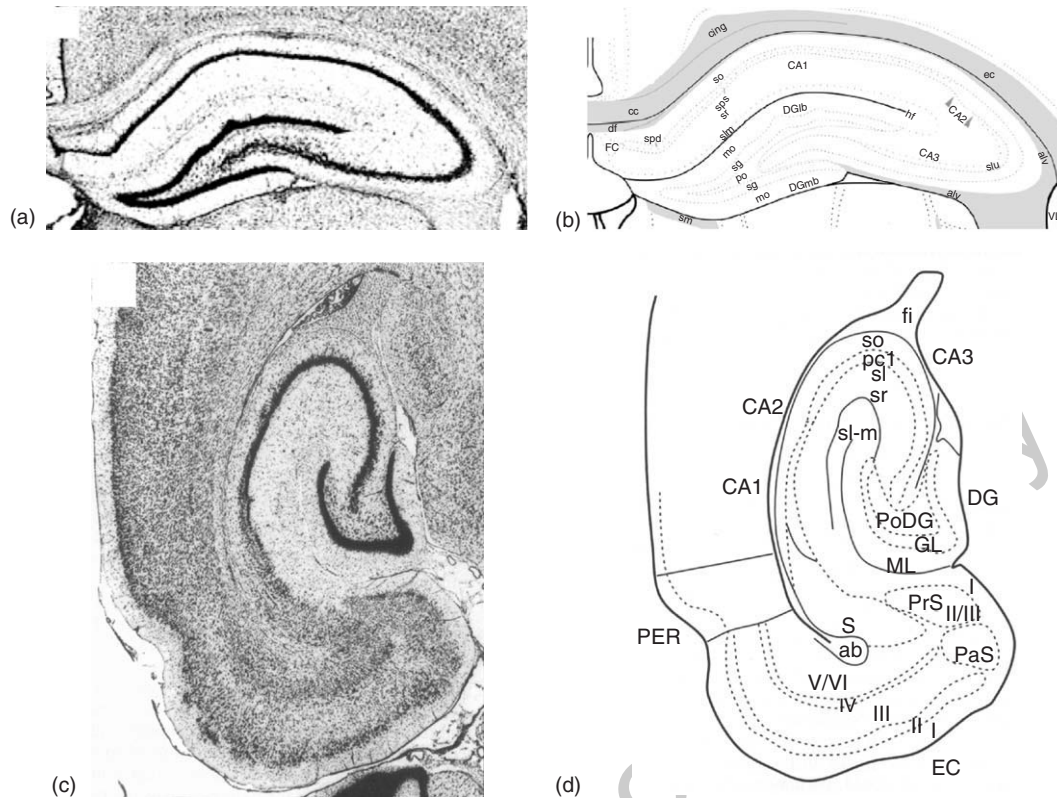


Figure 4 Laminal organization of rat hippocampal formation. a, Photomicrograph of histologically stained tissue of transverse section of the dorsal hippocampus (coronal plane); b, corresponding line drawing; c, photomicrograph of histologically stained tissue of transverse section of the ventral hippocampus (horizontal plane); d, corresponding line drawing. The strata of the hippocampus shown are stratum oriens (so), pyramidal cell body layer (spd, sps, or pcl), stratum lucidum (sl), stratum radiatum (sr), and stratum lacunosum-moleculare (slm). The strata of the dentate gyrus shown are the molecular layer (mo), granule cell body layer (gl or sg), and the hilus or polymorphic region (po). The tightly packed and orderly aligned pyramidal and granule cell bodies result in a darkly stained C- or V-shaped formation in the hippocampus or dentate gyrus, respectively. ab, angular bundle; alv, alveus; cc, corpus callosum; cing, cingulum; DGmb, dentate gyrus lateral or enclosed blade; Dgmb, dentate gyrus medial or free blade; EC, entorhinal cortex (layers I–VI); fi, fimbria of fornix; hf, hippocampal fissure; PaS, parasubiculum; PER, perirhinal cortex; PrS, presubiculum (layers I–III); S, subiculum; VL, lateral ventricle. Panels a and b from Swanson, L. W. (2004), *Brain maps: structure of the rat brain* (3rd edn.), Amsterdam: Elsevier Academic Press.; panels c and d from Witter, M. P. and Amaral, D. G. (2004), Hippocampal formation, In: Paxinos, G. (ed.) *The rat nervous system* (3rd edn.), pp. 635–704. Amsterdam: Elsevier Academic Press.

neuronal survival, a cross-sectional brain slice of the hippocampus and dentate gyrus maintains many functional features of an intact hippocampal circuit. The *ex vivo* electrophysiological study of hippocampal slices has been instrumental in deciphering the cellular and molecular correlates of hippocampal-dependent learning (Figure 5b).

Principal Neurons

All the principal cells of the hippocampal formation (pyramidal and granule cells) are believed to be glutamatergic. Pyramidal cells have a distinctly pyramidal or tear-drop shape. Pyramidal cells in CA3 and CA2 have larger cell bodies (approximately 25 μm in diameter) than those in CA1 (approximately 15 μm in diameter) (Figure 6). Separate multibranching dendritic trees emerge from the apex and base of

each cell. The base of the cell is defined by the surface from which the axon emerges, and the separate dendritic trees are referred to as apical and basilar dendrites, with each cell having one or two apical dendrites and several basilar dendrites. All hippocampal pyramidal cells are aligned in the same orientation, with the apical dendritic trees radiating toward the center of the C-shaped semicircle of cells (filling the stratum radiatum). The basilar dendrites extend in the opposite direction (filling the stratum oriens). Hippocampal pyramidal cell axons penetrate the stratum oriens and travel as part of the alveus to distal hippocampal or subcortical targets.

Granule cells of the dentate gyrus have small spherical or ovoid-shaped cell bodies (approximately 8–15 μm in diameter). One moderately complex dendritic tree (filling the stratum moleculare) is attached to the pole of the cell opposite from where

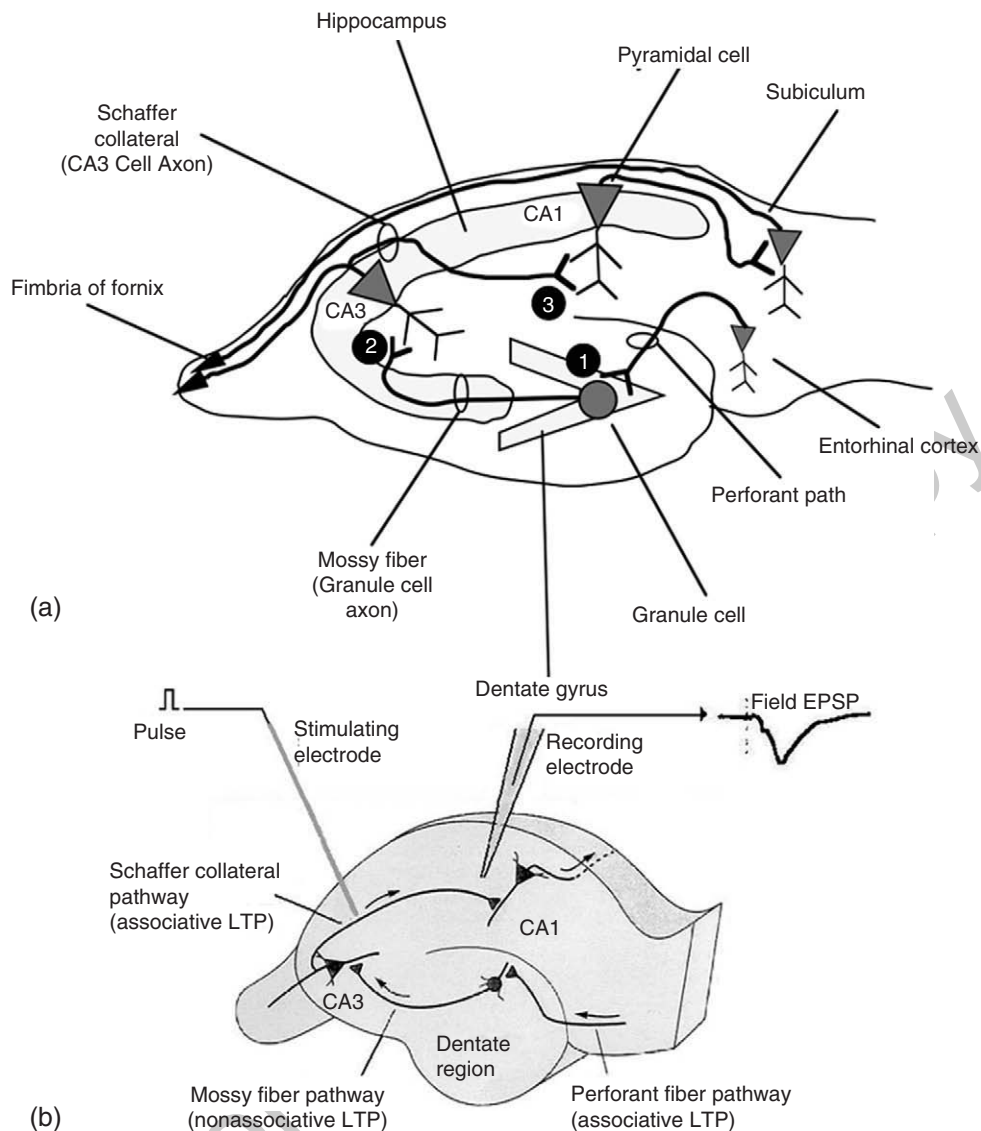


Figure 5 Hippocampal-formation trisynaptic neural circuit. a, An intact unidirectional trisynaptic neural circuit in a 250- to 500- μm transverse section of rat hippocampal formation (lamellae); b, *ex vivo* stimulation of a transverse slice of hippocampal formation placed in a chamber containing a solution of artificial cerebrospinal fluid to assess the electrophysiological activity in one component of the trisynaptic circuit. In (a) representative pyramidal cells (present in the entorhinal cortex, CA3, CA1, and subiculum) and a granule cell (in the dentate gyrus) that participate in the circuit are depicted. The three featured synapses of the circuit are numbered in the temporal order in which they are engaged by neural activity, starting with pyramidal neurons in the entorhinal cortex. In (b) a stimulating and recording electrode is applied to the tissue slice in order to assess electrophysiological activity within one component of the trisynaptic circuit. EPSP, excitatory postsynaptic potential; LTP, long-term potentiation. Adapted from Squire, L. R. and Kandel, E. R. (2000), *Memory, from mind to molecules*, New York: Scientific American Library.

the axon emerges and projects. There is also a population of large-diameter cells in the hilus region of the dentate gyrus called mossy cells that also appear to be glutamatergic. These cells receive input from the mossy fibers and project back to the dentate gyrus granule cells. Interestingly, mossy cells preferentially project bilaterally to granule cells at other levels of the longitudinal axis than that in which they reside.

The dendritic trees of hippocampal formation principal cells are densely covered with bulbous spines

(Figure 6). The head of these spines form the postsynaptic site for much of the excitatory input to these cells. There are especially large prominent spines on CA3 neurons and mossy cells called thorny excrescences, which form the postsynaptic site for the mossy fiber input from the dentate gyrus. Inhibitory synapses, largely arising from γ -aminobutyric acid (GABA)ergic interneurons, are mostly localized to the soma, dendritic shafts, and axonal initial segments of the principal cells.

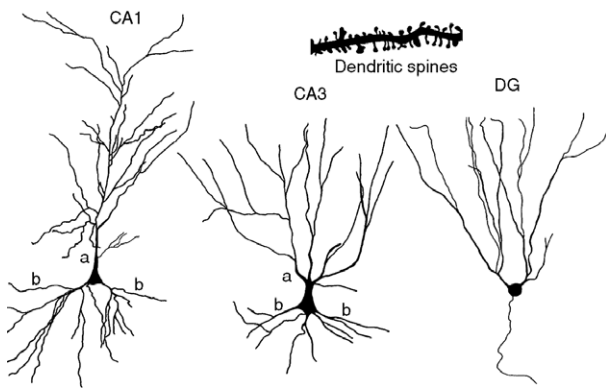


Figure 6 Hippocampal formation principal cells. Camera lucida tracings of representative CA1 and CA3 pyramidal cells in the hippocampus and a granule cell in the dentate gyrus (DG) from rat brain are shown. All three representative cells are oriented such that the axon emerges from the bottom of the cell body (an axon is clearly evident for the granule neuron). Multibranched apical (a) and basilar (b) dendritic trees are attached to the pyramidal cell body. The dendritic trees for the granule cell are attached to the upper portion of the cell body. A camera lucida tracing of an enlarged portion of a CA1 apical dendrite is also included. This tracing illustrates the dense presence of spines that cover the dendrites of these principal cells. Adapted from Gould, E., Woolley, C.S., Frankfurt, M., et al. (1990), *Gonadal steroids regulate dendritic spine density in hippocampal pyramidal cells in adulthood. Journal of Neuroscience* 10,1286–1291. © 1990 by the Society for Neuroscience.

Interneurons

There are various types of interneuron cell bodies scattered throughout all strata of the dentate gyrus and hippocampus. Most of these interneurons are presumed to be GABAergic, and they have been further categorized by the differential expression of various neuropeptides and calcium-binding proteins. Many of these interneurons have extensive axon collaterals and arborization that extend fairly long distances within both the longitudinal and transverse plane and form numerous synaptic contacts with principal cells. Although there are substantially fewer hippocampal interneurons than principal cells (probably totaling less than 1% of all hippocampal neurons), this pattern of connectivity allows them to have substantial effects on overall hippocampal function. Two of the better-characterized types of inhibitory interneurons are the basket cells and the chandelier or axoaxonic cells. The basket cells are so named because their multibranched axons form an extensive interwoven contact with the cell body of target pyramidal cells. The chandelier cells form strong synaptic contacts on the initial axonal segment of pyramidal cells. It should also be noted that there are many synaptic contacts between inhibitory interneurons as well as axodendritic contacts from principal cells. Thus, the

interneurons are interconnected in such a way as to mediate complex feedforward and feedback inhibition and disinhibition within the hippocampal formation.

Intrinsic and Extrinsic Neural Connections

A major source of neural input to the dentate gyrus, as previously described, is from the entorhinal cortex and constitutes the first component of the trisynaptic circuit. There are considerable reciprocal connections of the entorhinal cortex with other regions of neocortex, most notably the adjacent perirhinal cortex and the nearby postrhinal and piriform cortex. There are also substantial direct interconnections with the medial prefrontal, insular, and retrosplenial cortex. Thus, the entorhinal cortex is believed to provide the dentate gyrus and hippocampus with the rich multimodal sensory content of ongoing experience. In addition to the extensive input to the dentate gyrus, the entorhinal cortex also provides (via the temporal-ammonic pathway) direct monosynaptic parallel input to the CA3 region of the hippocampus, as well as direct input to CA1 pyramidal cells. Thus, both CA3 and CA1 neurons are in the position to integrate or compare direct and processed information from the entorhinal cortex. The projection of CA1 neurons back to the entorhinal cortex, either directly or via the subiculum, makes the entorhinal cortex the principal bidirectional interface between the hippocampal formation and various neocortical regions.

In addition to the trisynaptic circuit, there are extensive commissural and longitudinal associational connections within the hippocampus. The major source of these additional associational connections are provided by the non-Schaffer collateral branch of CA3 pyramidal cell axons, with additional contribution from CA2 pyramidal cells and mossy cells of the hilus.

There are other important neural inputs to the dentate gyrus and hippocampus from various populations of biogenic amine-containing neurons that may primarily modulate the general excitatory tone and neural synchronization within this structure. In addition, the CA1 region receives direct excitatory input from basal nuclei of the amygdala and midline nuclei of the thalamus. Interestingly, the amygdala input to the hippocampus is largely restricted to the ventral hippocampus.

The major output neurons of the hippocampal formation are pyramidal cells in CA1, subiculum, and deep layers of the entorhinal cortex. CA1 and subiculum pyramidal cells provide a large subcortical projection via the fornix to the septum and hypothalamus, with minor contribution from CA3 pyramidal cells. There are also strong direct connections of the

CA1 and subiculum with the medial prefrontal cortex. However, as previously indicated, there are more extensive indirect connections of the CA1 and subiculum with the prefrontal and other cortical areas via the entorhinal cortex.

Neurochemistry

Amino Acid Neurotransmitters

The excitatory neurotransmitter, glutamate, is released from hippocampal-formation principal cells and is therefore the neurotransmitter used by the perforant path, mossy fibers, and Schaffer collaterals. Glutamate receptor subtypes include the ionotropic receptors (iGluRs), which directly gate cation channels and are named after the ligands that preferentially bind to them: *N*-methyl-D-aspartate (NMDA), α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate. All the iGluRs are present in the excitatory pathways of the hippocampus. AMPA and kainate receptors mediate fast excitatory postsynaptic potentials (EPSPs), and NMDA receptors mediate slower EPSPs. All the iGluRs open Na^+ and K^+ channels. NMDA as well as some AMPA and kainate receptors are also permeable to Ca^{2+} . The NMDA receptor is unique in that channel permeability is both ligand- and voltage-dependent.

There is also a family of metabotropic glutamate receptors (mGluRs) that are coupled to guanine nucleotide-binding proteins (G-proteins). mGluRs have both pre- and postsynaptic localization and can coexist in the postsynaptic density with iGluRs. Postsynaptically, mGluR regulate synaptic transmission by stimulating specific second-messenger cascades and generating slow synaptic responses. When expressed presynaptically, mGluR activation can modulate transmitter release.

The inhibitory neurotransmitter GABA can also act on both ionotropic and metabotropic receptors. GABA_A receptors are ionotropic and gate ion channels that are permeable to the anion Cl^- . GABA also binds a metabotropic receptor, GABA_B, which is coupled to a G-protein that, when activated, opens K^+ channels. When expressed postsynaptically, GABA_B receptor activation leads to a slow hyperpolarization. When expressed presynaptically, GABA_B receptor activation reduces neurotransmitter release.

Biogenic Amines

The major cholinergic input to the hippocampus is from the medial septal nucleus. Acetylcholine (ACh), similar to glutamate and GABA, can act on both ionotropic (nicotinic receptors) and metabotropic (muscarinic) receptors, both of which are expressed

in the hippocampus. Nicotinic ACh receptors are ligand-gated ion channels that mediate fast excitatory transmission via an influx of Na^+ and Ca^{2+} . Nicotinic receptors are expressed on both excitatory and inhibitory interneurons in the hippocampus and can be expressed pre- and postsynaptically. Muscarinic receptors are very densely expressed in the hippocampus, and different subtypes are differentially expressed on specific populations of neurons: M_1/M_3 on principal cells and M_2/M_4 on interneurons. The actions of muscarinic receptor activation can be excitatory or inhibitory, depending on the type of G-protein to which the receptor is coupled: M_1/M_3 are coupled to G_q (which stimulates phospholipase C), and M_2/M_4 are coupled to $G_{i/o}$ (which can inhibit adenylyl cyclase or activate a K^+ channel). Muscarinic receptor activation potentiates NMDA receptor activity, probably by the activation of the M_1 subtype. M_2 can be expressed as autoreceptors on cholinergic terminals. Acetylcholine is also known to regulate the release of dopamine, serotonin, and neuropeptides by the activation of presynaptic nicotinic and muscarinic receptors.

Cholinergic neurons that project to the hippocampus from the medial septal nucleus and the nucleus of the diagonal band of Broca contribute to the synchronous discharge of principal cells reflected by the prominent theta frequency hippocampal electroencephalograph (EEG). Theta is observed both during voluntary movement (Type 1, 8–12 Hz) and during alert immobility (Type 2, 4–6 Hz), although only Type 2 theta is sensitive to cholinergic manipulations.

Dopamine afferent terminals are observed in the ventral subiculum, in all strata of CA1, in the stratum oriens of CA3, and in the hilus of the dentate gyrus. The source of hippocampal dopamine comes from the midbrain ventral tegmentum and substantia nigra and there is some evidence for different populations of dopaminergic cells innervating dorsal and ventral hippocampal formations. Dopamine receptors comprise two types, D1-like (D1 and D5) and D2-like (D2, D3, and D4), and all are metabotropic. D5 is the most prominent D1-like receptor in the hippocampus and is coupled to G_s (which stimulates adenylyl cyclase). D5 receptors are expressed on pyramidal cells and can enhance NMDA- and AMPA-mediated currents. Dopamine D4 is the most prominent D2-like receptor in the hippocampus. D4 receptors are densely expressed on pyramidal neurons in CA1, on granule cells in the dentate gyrus, and on GABA interneurons. D4 receptors are coupled to $G_{i/o}$ and decrease NMDA-mediated excitatory transmission.

Norepinephrine innervation of the hippocampus arises primarily from the locus ceruleus, and the hippocampus contains one of the highest densities

of norepinephrine-containing terminals in the brain. Receptors for norepinephrine (adrenergic receptors) have been divided into two classes: α and β , which are further subdivided based on the specific G-proteins to which they are coupled. β -adrenergic receptors are coupled to G_s , while α_1 types are coupled to G_q and α_2 types to G_i . Electrical stimulation of the locus ceruleus produces an inhibition of hippocampal pyramidal neuron firing, followed by a transient increase in firing. The inhibition appears to be mediated by α_2 and the excitation by β receptors.

Serotonin (5HT) input to the hippocampus derives almost exclusively from the median raphe nucleus. Serotonin receptors in the hippocampus are preferentially expressed on calbindin-positive GABA interneurons, and the specific subtypes expressed include 5HT_{1A}, which is coupled to $G_{i/o}$; 5HT_{2A}, which is coupled to G_q ; and 5HT₃. The 5HT₃ receptor is an ionotropic receptor, the activation of which opens a nonspecific cation channel, resulting in fast depolarization. The activation of 5HT₃ receptors can thus inhibit the firing of pyramidal neurons by a GABA interneuron-mediated mechanism. There are also autoreceptors of the 5HT_{1B/D} subtype on serotonergic terminals that inhibit the release of serotonin. Intracellular recording studies show that the most prominent effect of serotonin application to the hippocampus is hyperpolarization of pyramidal neurons caused by an increase in K^+ conductance.

Histamine projections arise from the tuberomammillary nucleus of the hypothalamus. Histamine H₂ receptors are dense in CA1 and CA3 and are primarily located on pyramidal cell dendrites, but are also found on granule cells in the dentate gyrus. H₂ receptors are coupled positively to adenylyl cyclase, and the activation of these receptors causes strong excitation. Histamine H₁ receptors are mostly found in CA3, where their activation causes hyperpolarization. The H₁ receptor is coupled to stimulation of phospholipase C via $G_{q/11}$. H₃ receptors are also inhibitory (coupled to $G_{i/o}$) and are located on perforant path terminals in the dentate gyrus, where their activation can suppress glutamate secretion.

Other Neuromodulators

The hippocampus is rich in other neuromodulators, including neuropeptides, growth factors, cytokines, and endocannabinoids as well as their receptors. Neuropeptides are typically coreleased with classical neurotransmitters. Neuropeptides expressed in hippocampal neurons include cholecystokinin, somatostatin, neuropeptide Y, leptin, galanin, corticotropin releasing hormone, and the opioid peptides β -endorphin, enkephalin, and dynorphin. Receptors for the

gonadal and adrenal steroid hormones and thyroid hormone are also expressed in the hippocampus. Growth factors that are abundant in the hippocampus include brain-derived growth factor (BDGF), nerve growth factor (NGF) and fibroblast growth factor (FGF). Growth factors perform neurotrophic and neuroprotective functions and are critically involved in development and neuroplasticity. Cytokines regulate intercellular communication, including glial-to-neuronal and immune-to-neuronal communication. Cytokine ligands and their receptors found in the hippocampus include interleukin-1, tumor necrosis factor, and fractalkine. Eicosanoids are metabolites of arachidonic acid, which is derived from dietary linoleic acid. Several of the eicosanoids, including anandamide (arachidonylethanolamine) and arachidonoylglycerol, are known as endocannabinoids because they act on the cannabinoid receptor CB1. High levels of CB1 expression are found throughout the hippocampus.

Neuroplasticity

Long-term potentiation (LTP) reflects a cellular model of learning and memory, first described in rabbit hippocampus in 1973. LTP is induced by applying a brief high-frequency electrical stimulus to an excitatory synaptic pathway, such as the hippocampal Schaffer collateral pathway, the perforant pathway, or the mossy fiber pathway (Figure 5b). For periods of hours (*in vitro*) to weeks (*in vivo*) after this conditioning stimulus, a test stimulus can subsequently provoke an increased synaptic response that is 50–200% above baseline. In the Schaffer collateral–CA1 synapse and the perforant path–dentate gyrus synapse, LTP is dependent on the activation of the NMDA receptor and subsequent Ca^{2+} influx (associative LTP), whereas in the mossy fiber–CA3 synapse, LTP appears to be dependent on kainate receptors (nonassociative LTP).

LTP has four basic characteristics that resemble features of learning and memory:

1. Temporal specificity: the presynaptic cell must fire before the postsynaptic cell.
2. Cooperativity: many synapses must be active to induce LTP.
3. Associativity: a strong input can induce potentiation at a weakly activated, adjacent synapse on the same postsynaptic cell.
4. Input specificity: potentiation is only induced at the synapses that received the conditioning stimulation.

In contrast to the potentiation caused by brief high-frequency stimulation, prolonged low-frequency stimulation of a pathway induces a long-term depression

(LTD) of the synaptic response to a test stimulus. Like the typical LTP found in most pathways (but not the mossy fiber pathway), LTD is also dependent on the activation of the NMDA receptor. It is thought that different patterns of Ca^{2+} influx produced during LTP and LTD induction determine the differential responses to these stimuli; high-frequency stimulation results in a large Ca^{2+} elevation and activation of the Ca^{2+} /calmodulin-dependent protein kinase (CaMK) cascade, whereas the smaller but more prolonged Ca^{2+} elevation produced by low-frequency stimulation leads to activation of a phosphatase cascade.

Hippocampal Function

The hippocampal formation appears to play a uniquely pivotal role in the brain's ability to form rapid and long-lasting associations between environmental stimuli in a way that allows for the learning of new concrete and abstract factual information (declarative memory) and detailed recall and recognition of events and places (episodic memory). The hippocampus in rodents appears to have an especially important role in learning the spatial configuration of places. Many CA1 and CA3 pyramidal cells behave as place cells; on initial exposure to a new environment, these cells acquire within several minutes the ability to increase their neuronal firing rate whenever the rat returns to a particular place in that environment.

The role of the hippocampus in stress response is less clear. As part of the limbic system, the involvement of the hippocampus in the generation of a stress state has often been presumed, but its anatomical neighbor, the amygdala, appears to play a much more important role than the hippocampus in this process. The cells of the hippocampus, however, appear to be especially sensitive to the effects of various stressors, perhaps in part due to their high expression of adrenal steroid receptors. Although the hippocampus may not be directly involved in the generation of a stress state, in the rat its more ventral regions contribute regulatory influences on hypothalamic-pituitary-adrenal (HPA) axis activity. Whether the primate hippocampus also has direct modulatory effects on the HPA axis remains to be determined.

See Also the Following Articles

Glucocorticoids – Adverse Effects on the Nervous System; Hippocampus, Corticosteroid Effects on; Hippocampus, Overview; Learning and Memory, Effects of Stress on; Memory and Stress; Neurogenesis; Steroid Hormone Receptors; Glucocorticoid Effects on Memory: the Positive and Negative.

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