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Hippocampus: Micro-Organ in Brain

Gehad Magdy Mohamed, Laila Mostafa EL Shal, Mohamed Abdel AL-Rahman Shaheen, Samar Mohamed Reda

Medical Histology and Cell Biology Department, Faculty of Medicine, Zagazig University

Abstract

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. 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. Ever since the 1957 report of the case study H.M., who famously lost the ability to form new, declarative memories after surgical removal of the hippocampus and nearby temporal lobe structures to treat intractable epilepsy, the hippocampus has been at the forefront of research into the neurobiological bases of memory. This research led to the discovery in the hippocampus of long-term potentiation, the pre-eminent model of the cellular basis of memory. Furthermore, the discovery of place cells, head direction cells, and grid cells in the rodent hippocampal formation established a firm foundation for the notion that the hippocampus plays a critical role in memory formation by providing the brain with a spatiotemporal framework within which the various sensory, emotional, and cognitive components of an experience are bound together. This framework allows the experience to be stored in such a way that it can be later retrieved as a conscious recollection of that experience.

Keywords: Hippocampus, brain, central nervous system.

Full-length article **Corresponding Author* e-mail: *dr.gegeabdelaziz@gmail.com*

1. Introduction

The hippocampus is a temporal brain structure belonging to the limbic lobe. Terminological discussions have complicated its anatomical definition, but it is now accepted that hippocampus consists of two allocortex laminae: the gyrus dentatus and the cornu ammonis, one rolled up inside other, creating a bulge in temporal horn of lateral ventricle. The hippocampal region is a prominent component of mammalian nervous system, which has attracted attention of neuroscientists since beginning of formal study of nervous system. Much of available information concerning the cellular organization and intrinsic connectivity of hippocampal region has been obtained from studies in rat although studies in other species characterized field in its very early phase, as well as in mid and late 20th century [1]. In classical Golgi studies [2], data from a number of species and developmental stages were described in early studies. In second half of last century, experimental animals reported on include the guinea pig, cat and macaque monkey, with additional but more fragmented reports on a variety of other species including dog, pig, mouse, and gerbil.

During the last part of the previous century the field went through an interesting change in focus, with emphasis increasing on the genetic approaches to understanding functional organization of the region. First by using a variety of inbred strains of both rats and mice showing behavioral and correlated structural differences [3], and later by increased usage of transgenic mice, the perspectives and potentials of field has changed dramatically [4]. Irrespective of the great potential of the use of transgenic mice, detailed knowledge of the architecture of the brain or parts of the brain forming functional networks within wild-type animals is required to understand its function and field has not yet witnessed a parallel increase in focus on architecture hippocampal region in mouse. It has essentially been assumed that architecture of mouse hippocampal region is a somewhat smaller replica of that of rat. Here, a summary of available data in mice is provided, indicating that this assumption is not that far off, although particular strain-differences in mice may be an important factor to consider [5].

1.1. Embryology

Human brain development is a prolonged process that begins in the third gestational week (GW) with the differentiation of the neural progenitor cells. The neuroectoderm gives rise to neural crest cells and neural tube .The first sign of neural tube development is appearance of two ridges that form along two sides of neural plate. The neural progenitor cells lie between two ridges. Over course of several days, ridges rise, fold inward and fuse to form a hollow tube (Fig. I). Fusion begins in the center of developing neural tube and then proceeds in both cephalic and caudal directions. The anterior neuropore at most cephalic end of the neural tube and the posterior neuropore at caudal end, are last segments to close [6]. The cephalic end of tube begins to expand forming the three primary brain vesicles. The most

anterior of these embryonic brain vesicles is called the "prosencephalon" which is the embryonic precursor of forebrain. The middle vesicle is "mesencephalon" which is precursor of midbrain structures. The most posterior vesicle is "rhombencephalon" which will become hindbrain. In fifth week, the prosencephalon divides into "telencephalon" and "diencephalon", and rhombencephalon divides into "metencephalon" and "myelencephalon".

The mesencephalon does not further divide (Fig.II). These five subdivisions establish the primary organization of the central nervous system (CNS) [7]. The Telencephalon gives rise to cerebral hemispheres, caudate, putamen, Amygdaliod, claustrum, lamina terminalis, olfactory bulbs and hippocampus [8]. The hippocampus is a deep structure hidden between the mesencephalon and medial aspect of temporal lobe. Three important changes are necessary for the complex shape and location of hippocampus: Firstly, Rotation of the lateral parts of developing telencephalon, forming the parietal, occipital, and temporal lobes, then the hippocampal sulcus invaginates into the medial wall of temporal lobe. Finally, hippocampal sulcus rotates along a longitudinal axis of the hippocampus, forming a complex structure that is present in the medial aspect of the temporal lobe [9]. The neocortex is mostly composed of the six cell layers, makes up the majority of the cerebral cortex. Early fetal life distinguishes the development of a flat cortical plate along the medial wall and floor of the temporal horn, which later becomes the mesial temporal structures.

These structures are made of a more primitive allocortex with three, four, or five cell layers. The different components of hippocampus grow at different rates, leading to the neocortex's enlargement and gradual in folding of its components. The hippocampal sulcus, which initially forms between the dentate gyrus (DG) and Cornu Ammonis (CA) and then moves to a position between the dentate gyrus and subiculum, is the site of the in folding. The hippocampus sulcus eventually disappears [10]. Neurogenesis is completed by birth in most of brain regions, but the dentate gyrus represents a clear exception in the mammalian brain because its main neurons, granular cells, proliferate during an extended period that begins during gestation and continues into the postnatal period. However, division of hippocampal pyramidal cell division is completed before birth; the structure of the pyramidal cells is simple at birth. The pyramidal neuron undergoes process of postnatal maturation and proliferation of their axonal connections and dendrites [11]. Multi potent progenitor cells reside below granule cell layer of dentate gyrus in the adult mammalian hippocampus and give rise to newborn granule cells that mature and functionally integrate into neuronal microcircuits [12].

1.2. Anatomy

Limbic system is a group of structures in brain that controls emotions, motivation, olfaction and behavior. The limbic system is also involved in formation of long-term memory. Structures of limbic system are found deep inside brain, immediately below temporal lobes. The limbic system consists of several interconnected components, including thalamus, hypothalamus, basal ganglia, cingulate gyrus, hippocampus, and amygdala [13]. Hippocampus is posterior part of limbic lobe while frontal part is amygdala [14]. The hippocampus is a part from larger structure called hippocampal formation (HF), term hippocampal formation includes dentate gyrus, Ammon's horn, subiculum, presubiculum, parasubiculum and entorhinal cortex. Hippocampus is considered a primitive type of cortex called allocortex (allo meaning odd, different or strange cortex) or archicortex (archi-meaning old cortex) .The hippocampus is a trilaminate archicortex, which made up of upper and lower plexiform layers, and in between these, there is a pyramidal cell layer [15-16]. Shape of hippocampus in gross dissection looks like a seahorse (genus Hippocampus) on basis of which structure is termed as 'Hippocampus'. The hippocampus also called 'Ammon's horn' because C-shaped coronal section of hippocampus mimics ram's horn; term 'Ammon's horn derived from Egyptian deity with ram's head [17]. In adult humans, volume of the hippocampus on each side of the brain is about 3-3.5 cm3 as compared to 320-420 cm3 for the volume of the neocortex. Thus, hippocampus is 100 times smaller in volume than cerebral cortex [18].

The hippocampus is a convex elevation of gray matter tissue within the parahippocampal gyrus inside the inferior temporal horn of the lateral ventricle. It was described as a curved and recurved sheet of the cortex that folds into the temporal lobe's medial surface. The hippocampus has three distinct zones: the dentate gyrus, the hippocampus proper, and the subiculum .The dentate gyrus and hippocampus proper (Cornu Ammonis) form two C-shaped rings that interlock (Fig.III). The subiculum is a transition zone, linking the hippocampus proper with the dentate gyrus [9]. Hippocampal orientation and curvature varies between different species. In species with a clearly developed temporal lobe as humans and monkeys, the hippocampus is more ventrally and anteriorly positioned. While in rats, the hippocampus looks more like a c-shaped structure positioned in the caudal third of the hemisphere. The hippocampus consists of three major subdivisions, which can be easily recognized in all species hippocampus, dentate gyrus and subiculm [20]. In axial and sagittal plane, it can be divided into three segments: head or anterior segment, the body or intermediate segment and tail or posterior segment [21]. Cornu Ammonis of the hippocampus can be subdivided into four areas CA1, CA2, CA3, and CA4 [22-23].

The CA1 is largest region and is bordered laterally by presubiculum and medially by CA2. 90% of the neurons in CA1 are pyramidal cells, or glutamatergic projection neurons, with interneurons making up the remaining 10%. In the direction of dentate gyrus, CA2 layer is present. It is medially and laterally limited by CA3 and CA1 layers. CA3 portion is directed towards hilus of dentate gyrus and is limited medially by CA2 layer. CA2 of cornu ammonis receives input from the supramammilary region of hypothalamus but lacks input mossy fires from dentate gyrus [24]. Dentate gyrus z not generally divided into subregions. In rodents, it tends to have more of a "V" shape septally and more of a "U" shapes temporally. Portion of granule cell layer that z located between CA3 field and CA1 field (separated by the hippocampal fissure) is called suprapyramidal (above CA3) blade and portion opposite to this, infrapyramidal (below CA3) blade. Region bridging two blades (at the Apex of the "V" or "U") is called crest (Fig .IV) [25]. Dentate gyrus consists of three layers, arranged from outside in: molecular layer, granular layer, and polymorphic layer. Dentate gyrus is semilunar in shape; convexity of which is directed towards molecular layer while concavity faces Cornu Ammonis.

It is input channel of the hippocampal formation [27]. The dentate gyrus is also one of only two regions in brain known to house neural stem cells that are capable of differentiating into new neurons throughout adulthood [28]. The subiculum is the medial and superior margin of the parahippocampal gyrus and attached with Cornu Ammonis. Parahippocampal gyrus is a gray matter structure that creates transition area between temporal lobe's basal and mesial parts. It is where the Cornu Ammonis continues inferomedially [10]. White matter fibers from hippocampus collect on its superior surface to form alveus, and then collect medially into condensed bundles as fimbria which is continuous posteriorly with fornix [29]. The superior surface of hippocampus situated within cavity of lateral ventricle and, is covered by ependymal cells called the alveus. The fornix which is main outflow bundle from hippocampus, connects hippocampus to mammillary bodies wraps around the thalamus, where it then becomes separated by choroid fissure and choroid plexus [30]. The hippocampus is substantially stimulated by activation of amygdala, hypothalamus, septum, and mammillary bodies because of its strong connections to these regions. Anterior thalamus, hypothalamus, and larger limbic system receive strong outgoing signals from hippocampus, particularly through fornix [9].

The entorhinal cortex (EC) is the greatest source of hippocampal input and target of hippocampal output. It is primary "interface" between the hippocampus and other parts of brain as it is strongly and reciprocally connected with many other parts of cerebral cortex [31]. Hippocampal input circuits are mediated by EC neurons in the superficial layers (layers II and III), providing inputs to all subfields of the hippocampus. In contrast, hippocampal output projections from CA1 and the subiculum terminate in the deep layers of EC (layers V and VI), which in turn project to other brain regions [32]. The subregions of hippocampus are connected by two principal neural circuits: the trisynaptic circuit and the monosynaptic circuit. The trisynaptic circuit forwards information from the entorhinal cortex to the dentate gyrus via the perforant path, which perforates through the subiculum. Information then flows from the dentate gyrus to CA3 via the mossy fiber pathway (so named for the extensive branching of its axons). Finally, information flows from CA3 to CA1 along bundles of axons known as Schaffer collaterals. The circuit is completed by outbound projections to the subiculum and the entorhinal cortex. The monosynaptic input bypasses the dentate gyrus and CA3 and instead transmits information directly from the entorhinal cortex to CA1 [33].

1.2.1. Blood supply and lymphatic drainage

The arterial supply of hippocampus involves the branches of the posterior cerebral artery with some contributions coming from the anterior choroidal artery). The arteries of the hippocampus are termed in accordance to their site of distribution. The head and uncus are provided by the anterior hippocampal artery; the body is supplied by the middle hippocampal artery, whereas the posterior hippocampal artery provides the tail of the hippocampus. The arteries supplying the hippocampus are located outside the ventricular cavity. All these arteries enter the hippocampus at the level of dentate gyrus. The awareness about the anatomy of vascularization of the hippocampus is very important that evidence suggests that the majority of patients with AD have mixed dementia, with both classic AD neurodegenerative pathology as well as cerebrovascular pathology [34]. Large pyramidal cells of the CA1 (an area known as Sommer's sector) are extremely sensitive to the oxygen lack; these cells necrose within a few minutes in compromised blood supply.

In a condition leading to cerebral ischemia, subject may lose the memory of the preceding few hours of the incident [24]. Intrahippocampal veins initially drain into two venous arch structures located in fimbriodentate sulcus and superficial hippocampal sulcus may be called the venous arch of fimbriodentate sulcus and the venous arch of superficial hippocampal sulcus. These two arches join together at their anterior and posterior extremities. The anterior extremity of these arches flows into inferior ventricular vein (often called vein of temporal horn), and posterior extremity reaches medial atrial vein. Both inferior ventricular and medial atrial veins are tributaries of basal vein [35]. Recent studies demonstrated that cerebral lymphatic system exists and consists of two parts: meningeal lymphatic vessels (MLVs), located in dura mater, and glymphatic system "glia-lymphatic" system, situated in brain interstitium. MLVs transport mixture of Cerebrospinal fluid (CSF) and interstitial fluid (ISF) from brain to deep cervical lymph nodes. The glymphatic system provides a perivascular passage way along which CSF and ISF are quickly exchanged [36].

1.3. Physiology

The physiology of hippocampus is unique and provides region with a high level of plasticity that is important for learning and memory; hippocampus and, in particular CA1 layer (output layer), has highest concentration of N-Methyl-D-aspartate (NMDA) receptors in the brain. Declarative learning and memory require relatively high levels of plasticity, which are enabled by action of glutamate receptors known as NMDA receptors, which support long-term potentiation (LTP) mechanism [37]. Hippocampus is a key structure for experience-dependent information storage and memory formation. Synaptic plasticity in hippocampus is an essential mechanism underlying experience-dependent learning and memory processes. Transforming short-term memory into long-term memory is one of hippocampal roles. Via intrinsic hippocampal circuitry, a unidirectional sequence of synaptic connections maintains long-term memory. Emotional integration and recent memory trace are thought to be processed via Papez circuit [38]. Papez circuit includes hippocampus, fimbria, and fornix, and mammillary body, anterior nucleus of thalamus and cingulate gyrus. Entorhinal cortex receives sensory information from association areas of frontal lobe, parietal lobe, and temporal lobe. Information is converted into memory through Papez circuit [39]. Short-term memory (episodic memory) facilitated by unidirectional activation of synaptic connection in following ways:

- Information from the limbic system and neocortex activates the entorhinal cortex (parahippocampal gyrus).
- Stimuli pass from the entorhinal cortex to the dentate gyrus via perforant path and then pass through the CA3 area.
- Schaffer's collaterals from CA3 transfer stimuli to the CA1; then CA1 efferent synapse at the subiculum.
- Efferent fibers from subiculum again project back to entorhinal cortex [24]. There are 2 prominent pathways: For learning and memory loop polysynaptic and direct pathway.

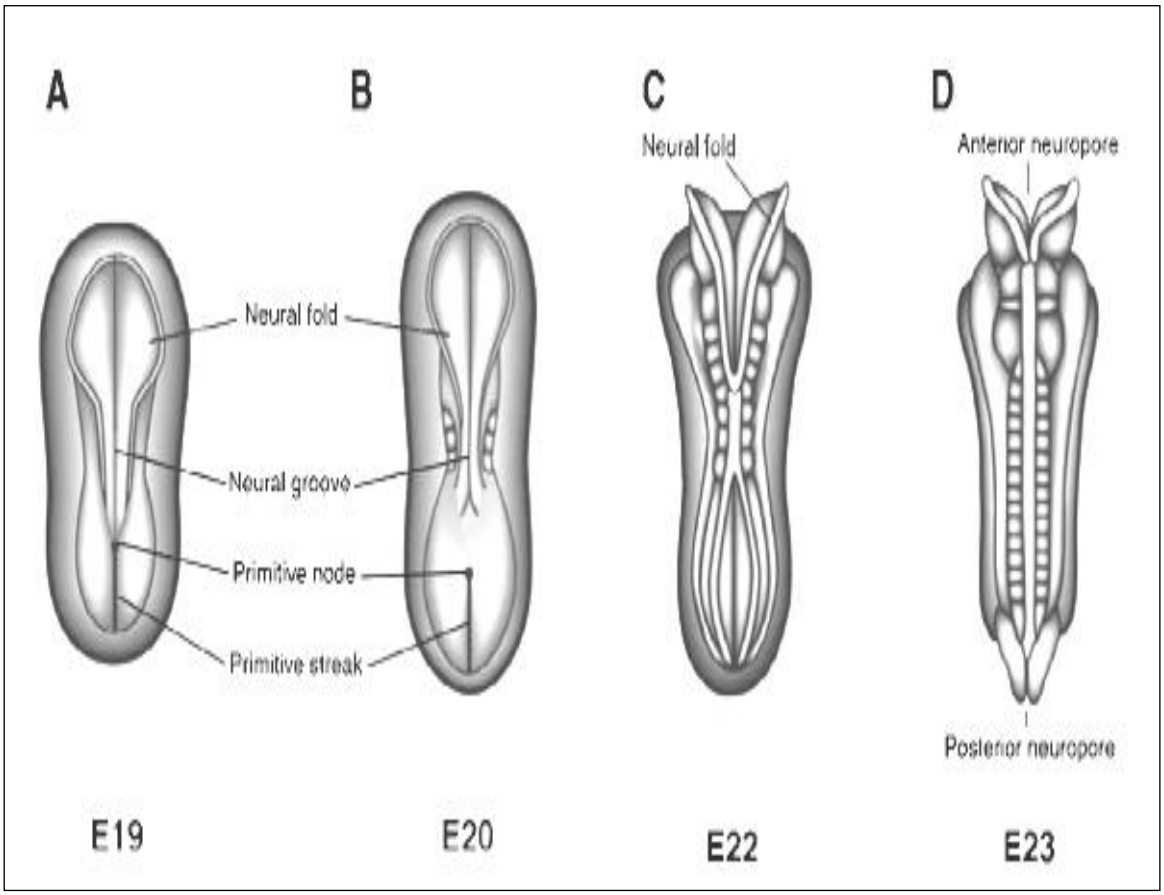

Figure 1. Shows neural tube development; appearance of two ridges. Then fuse together at its center then continues in both the cephalic and caudal directions [6].

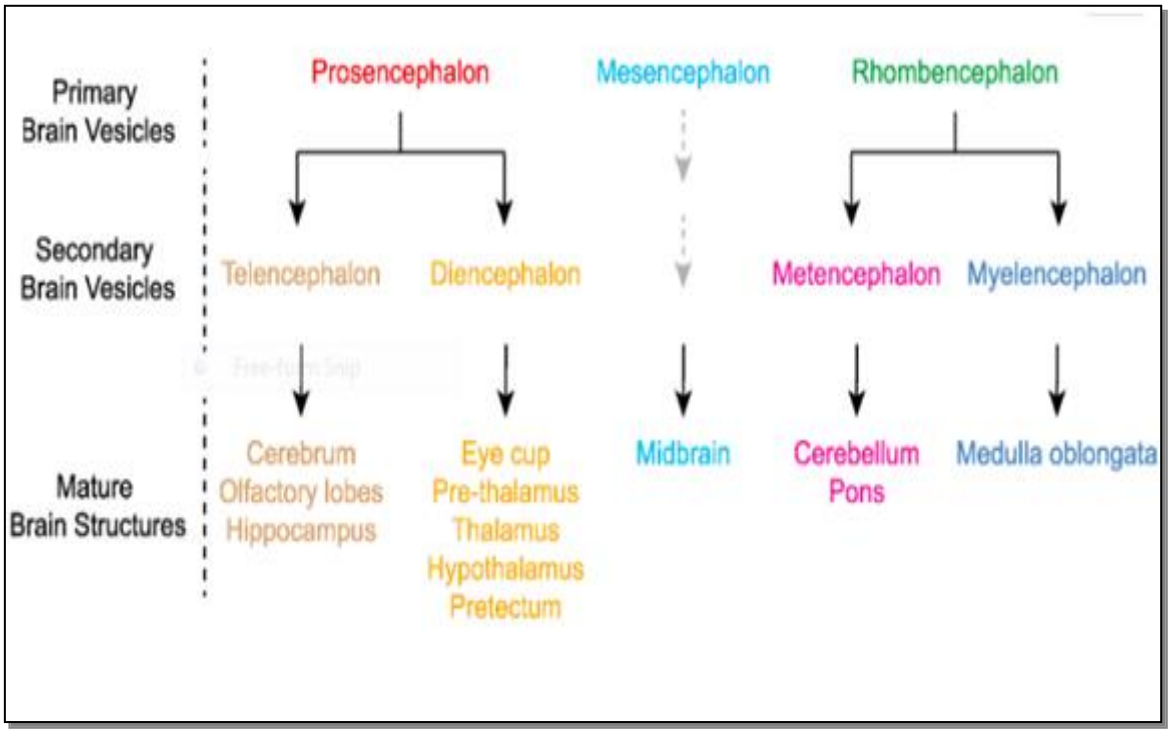

Figure 2. Shows the genesis of the development of CNS and derivatives from primary and secondary brain vesicles [7].

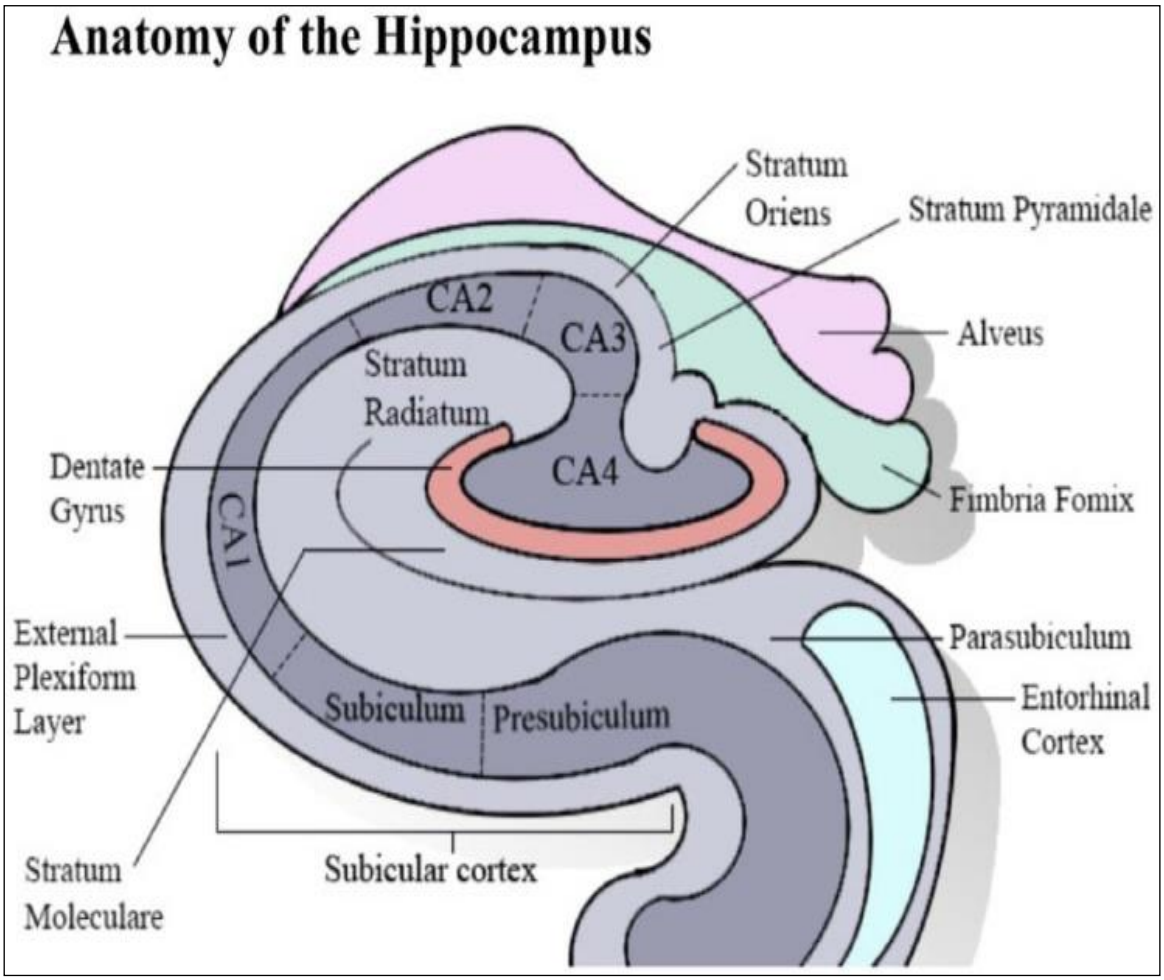

Figure 3. Showing anatomy of hippocampus with key structures (CA, DG and subiculum) [19].

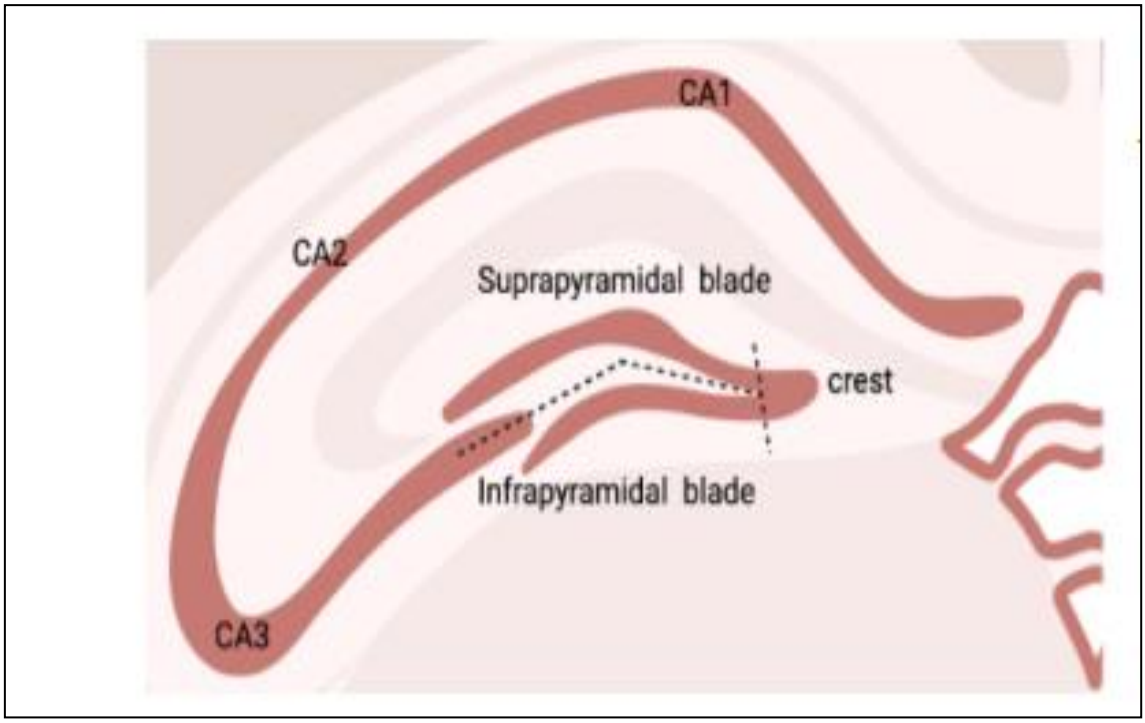

Figure 4. Shows the dentate gyrus anatomical portions; upper, lower blades and crest in relation to pyramidal cell layer of CA3 [26].

2. Conclusions

In polysynaptic pathway, hippocampus gets afferent connections from parietal, temporal, and occipital areas via entorhinal cortex and then to dentate gyrus→CA3→ CA1→ subiculum→ alveus→ fimbria→ fornix→ mammillothalamic tract→ anterior thalamus→ posterior cingulated→ retrosplenial cortex. In direct intra-hippocampal pathway, it gets its input from perirhinal and entorhinal area to CA1. Polysynaptic pathway is important in semantic memory; includes all our knowledge of facts and concepts while direct intra-hippocampal pathway play a role in episodic (personal experiences and specific events) and spatial memory related to acquisition [40-41]. Term of place cell refers to Pyramidal cells of the CA1, CA2, and CA3 regions, as well as granule cells of DG, fire selectively when rats occupy one or more specific locations in environment correlate with hippocampal neural activity. Discovery of these cells prompted theory of hippocampus that forms a cognitive map of environment [17].

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