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Review Article

Rat Hippocampus – Development and Morphological Organization

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Abstract

This article describes the formation of the rat hippocampus and its morphofunctional organization. The above information on the development and morphological organization of the rat hippocampus provides a basis for further study of this section of the cerebral cortex in health and in various pathologies and allows extrapolating the obtained experimental data to humans in those aspects that are not associated with the second signaling system, unique to humans.

Key words: rats, hippocampus, neurons, ontogenesis.

Introduction

The cerebral cortex is the highest part of the central nervous system. It represents the youngest phylogenetically and the most complex morphofunctional organization of the brain region. This is the place of the highest analysis and synthesis of all information entering the brain. This is where all complex behaviors are integrated. The cerebral cortex is responsible for consciousness, thinking, memory, "heuristic activity" (the ability to generalize, discover). Among the many parts of the cortex, the hippocampus (ammo n's horn) occupies a special place. It provides spatial orientation and memorization of certain places in space [1], plays an important role in olfactory reactions, namely in memorizing smells [2].The hippocampus is essential in supporting learning and memory processes. In rats with damage to the hippocampus, the trained passive avoidance of communication deteriorates due to the fact that they are not able to localize objects in space, while the animals do not cope well with switching the skill. The most characteristic disorder in rats after hippocampectomy is the difficulty in developing delayed conditioned reflexes [1].

The rat is one of the important objects of experimental research, including in the study of the cerebral cortex in normal conditions and in various pathologies. To extrapolate the data obtained in animal experiments to humans, a clear understanding of the morphofunctional features of different parts of the rat cerebral cortex, including the hippocampus, is required.

The hippocampus is located deep in the cerebral hemispheres, is part of the temporal lobe and belongs to the olfactory brain. One of the classifications assigns the hippocampus, together with the olfactory cortex, to the ancient cortex (archicortex), and the other to the old (paleocortex) [3].

Development of the hippocampus

In the rat hippocampus, the pyramidal neurons of the CA3ab fields (on the 17th day of embryogenesis) are the first to differentiate, then the neurons of the CA1 and CA3c fields. Granular neurons of the dentate gyrus of the hippocampus are formed mainly during the first week after birth [5, 6 ,7].

Autoradiographic studies carried out on rat embryos have shown that the neuroepithelium, from which hippocampal neurons are formed, consists of three components. One gives rise to pyramidal cells. The second - to the granular cells of the dentate gyrus. From the third, the glia of the main fibers entering and leaving the hippocampus develops. The putative source of development of pyramidal neurons in the hippocampus is the bulge of the medial wall of the anterior cerebral bladder, which can be seen in 14-day-old rat embryos. Its neuroepithelium has a high level of proliferative activity up to the 19th day of intrauterine development [4]. The pyramidal neurons formed in the following days of embryogenesis leave this zone and migrate to the pyramidal layer. The CA1 field neurons migrate radially for four days to their destination. Although CA3 neurons differentiate earlier than CA1 neurons, they take longer to migrate as they bend around clusters of CA1 neurons. It is possible that the earlier time of emergence of CA3 neurons is associated with their longer migration. In newborn rat pups, many pyramidal cells still migrate into the corresponding layers [4, 5].

Granular neurons of the dentate gyrus develop from the neuroepithelium of the so-called "dentate notch" (anlage of the dentate gyrus). From the 19th day of embryogenesis until the moment of birth, proliferating cells migrate into the dentate gyrus, following a curved path around the edge of the hippocampus. On the 20-30th day after birth, stem cells in the hippocampus are preserved only under the granular layer [4].

The structure of the hippocampus

The hippocampus is composed of tightly packed ribbon-like cells that stretch along the medial walls of the inferior horns of the lateral ventricles of the brain in the anteroposterior direction (Figure 1). Both halves of the hippocampus are interconnected by commissural nerve fibers [4,5, 6].The hippocampal formation is subdivided into the "hippocampus proper" (fields CA1, CA2, and CA3), the dentate gyrus, and the subiculum. The hippocampus itself is divided into proximal large-cell and distal small-cell regions [7], and the CA3 and CA2 fields are equivalent to the large-cell region, and CA1 - to the small-cell region [8, 9] (Figure 1).

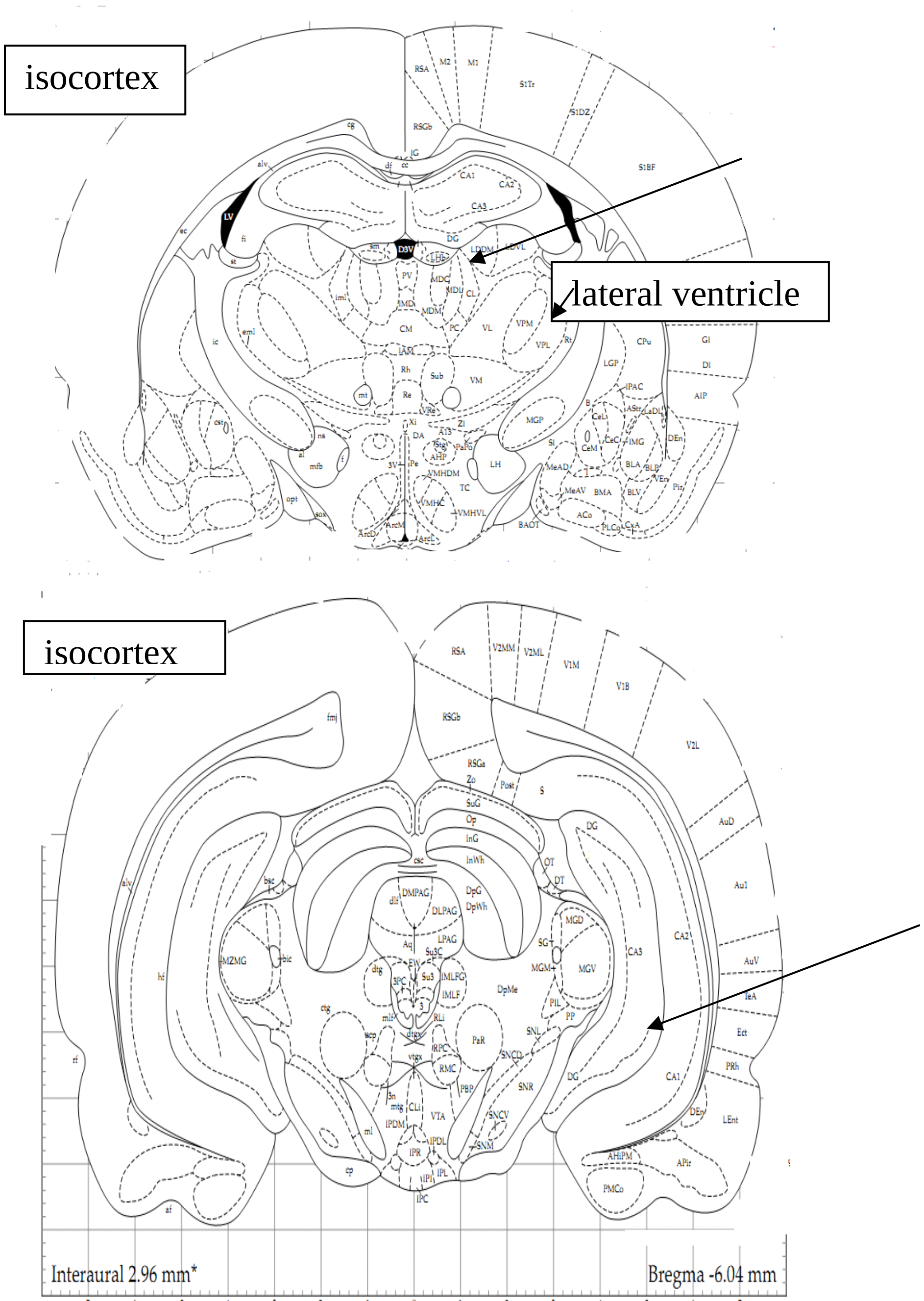

Figure 1. *Arrangement of fields (CA1, CA2 and CA3) and dentate gyrus (DG) of the hippocampus (shown by arrows) on the diagram of frontal sections of the rat brain [10]. A - Bregma - 2.56 mm, B - Bregma - 6.04 mm.*

According to modern histological nomenclature, three layers are distinguished in the hippocampus itself: 1) molecular (stratum moleculare), including eumolecular (substratum eumoleculare), lacunar (substratum lacunosum) and radial (substratum radiatum) sublayers; 2) pyramidal (stratum pyramidale) and 3) marginal (stratum oriens) layers (Figure 2) [11]. Layer organization is usually the same for all hippocampal fields.

The molecular layer contains the bodies of three types of non-pyramidal GABAergic neurons [12]. In the eumolecular sublayer lies a bundle of fibers heading from the subiculum, the afferent pathways from the entorhinal cortex and the nuclei of the median thalamus end, and in the lacunar sublayer there are axons going from the hippocampus to the subiculum. In field CA3, in contrast to fields CA2 and CA1, there is a narrow acellular zone located just above the layer of pyramidal neurons, where the axons of cells of the dentate gyrus (substratum lucidum) pass. At the distal end, these fibers form a bend that marks the border of the CA3 and CA2 fields. Substratum radiatum includes nerve fibers that provide connections between the CA3 and CA1 neurons.

The pyramidal layer is the main layer of the hippocampus proper. It contains pyramidal, basket, trilaminar neurons and candelabra cells. Dendrites of pyramidal cells are directed to both the molecular and the marginal layer [7]. Lorente de No (1934) noted differences in the dendritic organization of pyramidal cells in different parts of CA3 and CA1 and used this to further divide these fields into three subregions (CA3a, b, c, CA1a, b, c) [9].

The narrow, relatively cell-free marginal layer contains the basal dendritic branches of pyramidal neurons, as well as the bodies and dendritic branches of polymorphic (non-pyramidal) interneurons.

In the hippocampus itself, there are 8 types of neurons. The main ones, pyramidal, are cholinergic, and the rest are GABAergic [14]. Pyramidal neurons are located in the pyramidal layer. Their sizes and organization in CA3 change sequentially depending on their position along the CA3 axis. The cells of the proximal part, located near the dentate gyrus, have the smallest, and the neurons of the distal part of the CA3 field (near CA2) have the largest dendritic ramifications. CA2 contains a mixed population of both neurons with extensive dendritic branching, similar in size to those of the distal CA3, and cells with smaller dendritic branches, resembling the pyramidal neurons of CA1. 42-51% of the basal dendrites of CA3 pyramidal neurons are located in the stratum oriens, 34% of the dendrite branches of CA1 neurons extend into the same layer, and 18% of the apical dendrites of the same fields go to the stratum moleculare and lacunosum [12] (Figure 2).

In addition to pyramidal neurons, the pyramidal layer of the hippocampus contains a heterogeneous population of basket cells of various sizes and shapes [15, 16]. They have apical and basal dendritic ramifications. The axons of the basket neurons extend transversely from the cell body and form basket-shaped plexuses that synapse with the bodies of the pyramidal neurons of the hippocampus. Basket neurons receive excitatory impulses from pyramidal neurons, and they themselves exert an inhibitory effect on them. Pyramidal cells generate recurrent excitation, which is an important mechanism for memory formation [15, 16] (Table 1).

Neuron name	Bark layers (sublayers)	Afferent innervation	Efferent innervation	Mediator
Non-pyramidal interneurons	Molecular (stratum molecular)	Axons of neurons of the entorhinal cortex and nuclei of the thalamus, non-pyramidal interneurons of the molecular and marginal layers	Non-pyramidal interneurons of the molecular and marginal layers, dendrites of pyramidal neurons	GABA
Non-pyramidal interneurons	Lacunar sublayer (substratum lacunosum)	Non-pyramidal interneurons of the molecular and marginal layers	- // -	GABA
Non-pyramidal interneurons	Radial sublayer (substratum radiatum)	Non-pyramidal interneurons of the molecular and marginal layers	- // -	GABA
Pyramidal neurons	Pyramidal (stratum pyramidale)	Axons of granular neurons of the dentate gyrus, Schaffer's fibers, axons of basket cells and all other neurons of the molecular and marginal layers	Schaffer's fibers, entorhinal cortex neurons, basket neurons	Acetylcholine
Basket neurons	Pyramidal	Axons of pyramidal neurons	Pyramidal neurons	GABA
Trilaminar neurons	Pyramidal	- // -	Subiculum neurons	GABA

Candelabra cages	Pyramidal	- // -	Pyramidal neurons	GABA
Non-pyramidal interneurons	Regional (stratum oriens)	Non-pyramidal interneurons of the molecular and marginal layers	Pyramidal neurons	GABA

Table 1. *Neural and transmitter organization of the hippocampus proper*

There are different types of non-pyramidal interneurons. They are located in the molecular and edge layers. The overwhelming majority of them are considered to be local circuit neurons [17]. Dendrites of hippocampal interneurons go to the stratum oriens, and axons form synapses in the stratum moleculare [18, 19]. These cells form synapses with dendrites of pyramidal neurons, exerting an inhibitory effect on them [20, 21] (Table 1). Some of the interneurons of the CA1 field have rather extensive axonal branches along the transverse axis of the hippocampus, reaching the CA3 field and the dentate gyrus. Such cells are usually found in the marginal layer, their dendrites branching in the horizontal plane. The axons of these neurons form symmetrical synapses on the dendrites of pyramidal neurons and provide inhibitory feedback [15, 19].

Despite the fact that over the past decade a lot of information has appeared on the structure of hippocampal interneurons [15,19, 21,22,23], their functions have not yet been fully understood. Interneurons can excite or inhibit other cells and have an extremely variable number of excitatory and inhibitory inputs. Moreover, the overall effect of interneuronal transmission may differ depending on the type of interneuron and the postsynaptic structure with which it makes synaptic contact. Most of the non-pyramidal cells are GABAergic and have an inhibitory effect on the cholinergic pyramidal neurons of the hippocampus [24] (Table 1).

In addition, in the hippocampus there are interneurons with an additional terminal plexus of processes in the pyramidal layer, trilaminar neurons. Their dendrites entwine the dendrites of pyramidal neurons, and axons form extra-hippocampal synapses. Perikaryons of other interneurons are located in the pyramidal or radial layer and have a rather limited local network of axons that form synapses with pyramidal cell dendrites [20]. All hippocampal fields in the pyramidal layer also contain candelabra cells. Their dendrites form synapses on the dendrites of pyramidal neurons, and axons innervate the initial axonal segment of pyramidal neurons [21,22 ,23].

Dentate gyrus

The dentate gyrus (parahippocampus) in the front of the brain is located under the hippocampus itself, and in the back, medial to it. It has three layers. The deepest on the frontal sections is the molecular (stratum moleculare), then the granular layer (stratum granulare), and the topmost is the multiforme (stratum multiforme) (Figure 2). These layers contain 9 types of neurons (Table 2).

The molecular layer contains the bodies of small basket neurons, whose axons end on the basket cells of the granular layer, and dendrites do not leave the molecular layer [25]. The second type of neurons in the molecular layer are candelabra cells [26]. Their axons go into the granular layer, and their dendrites branch out within the molecular layer. These types of neurons receive impulses along the excitatory perforating pathway, are GABAergic (also contain parvalbumin) and have an inhibitory effect on granular neurons [18] (Table 2). In addition, dendrites of granular, basket and polymorphic neurons are located in this layer.

There are 2 types of neurons in the granular layer. Granular neurons have elliptical perikaryons. The branches of their dendrites are directed to the molecular layer [21]. Basket cells are located between granular and polymorphic neurons. Their axons entwine the perikaryons of granular cells [7], apical dendrites are directed to the molecular layer, and basal dendrites to the polymorphic layer. Granular neurons use glutamate and dynorphin as mediators, while basket neurons use GABA and parvalbumin [25]. Especially important is the fact that neurons of the granular layer continue their differentiation in adult rats [5] (Table 2).

There are five types of neurons in the polymorphic layer. The most common of them are bryophytes. Their perikaryons are pyramidal or polygonal. Dendrites form branches within the polymorphic layer, and axons end on other neurons of the same layer and on pyramidal neurons of the hippocampal fields. In addition to bryophyte cells, there are fusiform, small polymorphic, stellate neurons and candelabra cells (Table 2). They receive afferent innervation from mossy fibers, and their axons either form synapses within the polymorphic layer, or extend into the fields of the hippocampus, to its pyramidal neurons. All neurons of the polymorphic layer contain the GABA mediator and have an inhibitory effect on the pyramidal cells of the hippocampal fields and on the neighboring neurons of their own layer [27].

Neuron name	Bark layer	Afferent innervation	Efferent innervation	Mediator
Basket neurons	Molecular	Perforating pathway (axons of neurons in the entorhinal cortex)	Granular neurons	GABA / Parvalbumin
Candelabra cages	Molecular	- // -	Granular neurons	GABA / Parvalbumin
Granular neurons	Grainy	- // -	Dendrites of CA3 pyramidal neurons of the hippocampus	Glutamate / dynorphin
Basket neurons	Grainy	- // -	Granular neurons	GABA / Parvalbumin

Moss neurons	Polymorphic	Mossy fibers (axons of granular neurons)	Pyramidal neurons of the hippocampus, neurons of the polymorphic layer	GABA
Fusiform neurons	Polymorphic	- // -	Pyramidal neurons of the hippocampus, neurons of the polymorphic layer	GABA
Small polymorphic neurons	Polymorphic	- // -	Pyramidal neurons of the hippocampus, neurons of the polymorphic layer	GABA
Stellate neurons	Polymorphic	- // -	Pyramidal neurons of the hippocampus, neurons of the polymorphic layer	GABA
Candelabra cages	Polymorphic	- // -	Pyramidal neurons of the hippocampus, neurons of the polymorphic layer	GABA

Table 2. *Neural and transmitter organization of the dentate gyrus*

Pathways of the hippocampus

There are two main types of neural circuits in the hippocampus: trisynaptic and monosynaptic. In the trisynaptic chain, afferent innervation comes from the entorhinal cortex and enters the granular neurons of the dentate gyrus through the perforating pathway (it perforates the subiculum). Axons of granular neurons form bryophytes and form synapses with dendrites of CA3 pyramidal neurons. From CA3, impulses are transmitted to CA1 and CA2 by Shaffer's fibers (axons of CA3 pyramidal neurons). The axons of the CA1 pyramidal neurons through the subiculum form a feedback efferent connection with the entorhinal cortex.

The monosynaptic chain, bypassing the dentate gyrus and the CA3 field, transmits information directly from the entorhinal cortex to the CA1 pyramidal neurons [15, 19].

Thus, the above information on the development and morphological organization of the rat hippocampus provides a basis for further study of this section of the cerebral cortex in health and in various pathologies and allows extrapolating the obtained experimental data to humans in those aspects that are not associated with the second signaling system, unique to humans.

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