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Review

Adult neurogenesis. From circuits to models

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ABSTRACT

Our understanding of the hippocampus as a memory-encoding device is greatly helped by our knowledge of neuronal circuits and their plasticity. The trisynaptic hippocampal circuit carrying afferent input from the entorhinal cortex, controlled by a network of inhibitory interneurons and supplemented by modulatory subcortical inputs forms a platform for multiple forms of synaptic plastic mechanisms. Long-term potentiation of synaptic transmission in its various forms is an outstanding example of hippocampal ability to adapt to past neuronal activity. Adult neurogenesis is a profound plastic mechanism incorporating structural and functional changes that were previously thought to be present only in developing neural systems. These powerful forms of plasticity can mask experimental results by compensating for experimentally induced changes in the neurons or circuits. Circuit lesions have been one of the most common techniques in scientific investigations of the hippocampus. Although the effects of such lesions can be quite revealing and ground-breaking, in many cases the results are masked by compensatory mechanisms producing misleading results. This review will highlight such mechanisms and argue that the experimental results, in spite of their shortcomings, can be better understood when viewed in light of our knowledge of the neuronal circuitry, and with guidance by conceptual and computational models. Studies demonstrating a role of neurogenesis in pattern separation and memory interference are a good example of fruitful interaction between modeling and experimental approaches.

Contents

1. Why is circuit knowledge essential?

Adult neurogenesis is often portrayed as a developmental process within a predominantly adult brain environment. Although essentially correct, this representation is incomplete since it does not take the neuronal circuitry into account. In the hippocampus, the circuitry is paramount and our understanding of the hippocampal function is based upon neuronal interactions within this circuitry. The backbone of the hippocampal circuitry is the trisynaptic circuit (or loop) comprising the dentate gyrus (DG), CA3 and CA1. The inflow of impulses from the entorhinal cortex (EC) is propagated by excitatory synaptic relays in DG, CA3 and CA1 and back into EC, hence the loop. The function of various components of this loop has been studied in the standard hippocampal slice preparation, which includes a 500 μm thick slice of tissue with all three hippocampal regions and most of their synaptic interconnections [1]. Such hippocampal slices can be prepared by sectioning the hippocampus anywhere along its longitudinal axis, suggesting that this stereotypic arrangement of neuronal interconnections is repeated as a functional unit along the septo-temporal (dorsoventral in more common terminology) extent of the hippocampus (Fig. 1).

One obvious over-simplification of the trisynaptic circuit is the exclusion of inhibitory interactions. In reality, there exists a rich network of inhibitory interneurons supplying feedforward and feedback synaptic connections throughout the hippocampus and within DG in particular [2]. Uniquely, in DG, inhibition plays a direct role in neural signalling by acting on mature and immature

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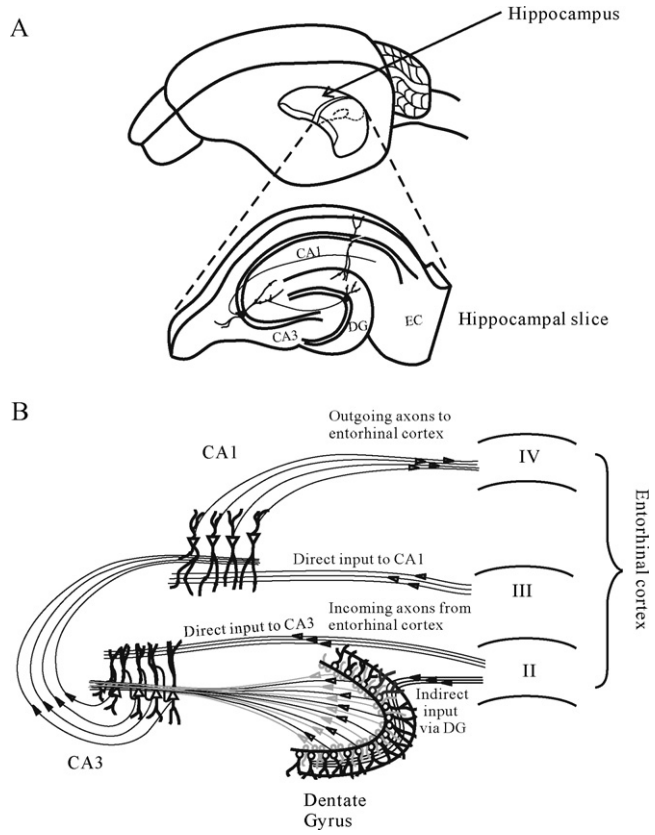

Fig. 1. Placement of the hippocampus in the brain and the general layout of the tri-synaptic loop. (A) Orientation of the hippocampus in the rat brain allows for visualization of a hippocampal slice as it would appear *in situ*. Each slice includes a portion of the entorhinal cortex (EC), the dentate gyrus (DG), field CA3 (CA3) and field CA1 (CA1). Thin lines represent axonal projections. (B) The EC layer II projects to DG and to CA3. These projections can be further subdivided into medial and lateral perforant pathways (see Fig. 4). EC layer III projects to distal dendrites of pyramidal neurons in CA3. The DG granule neuron (both mature and immature) axons stream from DG to the proximal dendrites of CA3. Immature neurons (grey) are typically lined along the inner border of granule cell layer. The CA3 neurons send axons to CA1 (Schaffer collaterals) and the CA1 neurons send axons to layer IV on EC. The direction of flow of impulses is shown by small arrowheads on the axons.

neurons as well as a modulatory role on neuronal development. To serve these two distinct yet interrelated roles there are several types of interneurons. Historically, the interneurons have been described based primarily on morphological criteria [3,4]. The differences among the cell types are in the location of their somata, branching pattern of their dendrites and axons. At least five types have been described and these are illustrated schematically in Fig. 2. The branching pattern of their axons is particularly extensive and revealing with respect to their possible functions as shown in Fig. 3. Considering the several examples of interneurons shown in Fig. 3 one sees striking differences in their termination fields. The first is an interneuron with its cell body in the hilus and an axon terminating within the outer two thirds of the molecular layer, corresponding to the distribution of the perforant path terminals on granule cell dendrites, called a HIPP interneuron. This type of interneuron could potentially inhibit the distal dendrites of both mature and immature granule neurons. The second, a HICAP interneuron, terminates in the inner one third of the molecular layer corresponding to the termination of axons of the collateral/associational pathway, and could potentially inhibit the proximal dendrites of the mature granule neurons, as well as large portions of the growing, immature neurons.

Next, consider cells illustrated in Fig. 3C. One interneuron has a cell body and dendrites in the outer molecular layer and extensive axonal branches in the same general region. This is an interneuron belonging to the MOPP category also shown in Fig. 2. The other interneuron's cell body is located in the inner molecular layer, but the profuse axonal branches are mainly found in the granule cell layer (GCL). The two interneurons shown in Fig. 3C show physiological coupling via electrical junctions [5]. The potential implications of such complex interconnections for neurogenesis are many. It is possible, for example, that the inhibitory interneurons with axonal projections within the GCL could influence neuronal progenitors and very immature, developing granule neurons. This influence could be synaptic, but could also be extrasynaptic and mediated by diffusion of GABA via the extracellular space. Other interneurons would have inhibitory effects via synaptic connections with dendrites of granule neurons in inner, middle or outer molecular layers, reaching progressively more mature neurons. The existence of extensive coupling among some of the interneurons [5] emphasizes yet another source of complex compensatory effects that could arise if some components of this circuit are removed. It is also worth mentioning that almost all inhibitory interneurons produce peptides co-transmitters in addition to GABA. These peptides could have additional, and not necessarily inhibitory, effects on new granule neurons at various stages of their development.

Electrophysiological data have so far indicated that immature granule neurons are at first contacted by dendritic GABA-ergic synapses [6]. This innervation could originate from the MOPP (neurogliaform) interneurons illustrated in Fig. 2C. Indeed, the results of Markwardt et al. [7] support a hypothesis that specialized interneurons form synapses on immature granule neurons and produce slow, depolarizing IPSPs consistent with the properties of neurogliaform cells [4]. This type of signalling could have a controlling influence on neuronal development.

In addition, the excitatory synaptic inputs within the DG are topographically distributed. For example, the cortical afferents terminating in the DG have a laminar layout with two major inputs synapsing in the two separate regions of the molecular layer [8]. The lateral perforant pathway originating from the lateral entorhinal cortex terminates in the outer molecular layer. This pathway also extends towards CA3 and CA1 fields, forming synapses with distal dendrites of pyramidal neurons. The medial perforant pathway, carrying the majority (>80%) of cortical inputs, originates in layer II of the entorhinal cortex and terminates in the middle molecular layer (Figs. 1 and 4). There are also septo-temporal variations in the projections and termination fields of these two pathways as well as notable species differences [3,9]. The inner molecular layer, just above the GCL, is occupied by associational/commissural inputs from the contralateral hippocampus. These are primarily axon collaterals of pyramidal neurons projecting from the hippocampus in the opposite side of the brain. Superimposed on these laminar inputs are complex termination zones of the afferents of the modulatory projections releasing acetylcholine, norepinephrine, serotonin and various peptides [3,8,10]. Cholinergic projection, in particular, originate mainly from the septum and the hypothalamus and terminate on proximal dendrites of granule neurons [3,11]. The axons of these pathways travel through the fornix and its extension the fimbria, to arrive in the DG as well as in the other regions of the hippocampus. In contrast, noradrenergic and serotonergic projections from the brain stem terminate mainly in the hilus and subgranular region, respectively [3]. There are also diffuse projections of noradrenergic, serotonergic and dopaminergic axons in the molecular layer. Some of these are known to make synapses on inhibitory interneurons as well as on dendrites of granule neurons [3,11].

All these complex projections, involving various transmitters, suggest that DG is not only a gateway into the hippocampus but also a filter and a modulator of the incoming signals. DG is also thought of as a "separator" of cortical inputs since the number of