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Review

Requirement of adult-born neurons for hippocampus-dependent learning

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ABSTRACT

A fundamental question in the field of adult neurogenesis relies in addressing whether neurons generated in the adult dentate gyrus are needed for hippocampal function. Increasing evidence is accumulating in support of the notion that hippocampus-dependent behaviors activate new neurons and that those neurons are highly relevant for information processing. More specifically, immature new neurons under development that have unique functional characteristics begin to emerge as a highly relevant population in the dentate gyrus network. This review focuses on how hippocampus-dependent behaviors activate adult-born neurons and how modulation and ablation of adult hippocampal neurogenesis alter spatial and associative memory. While several contradictory findings emerge when analyzing the literature, evidence in favor of a relevant role of adult-born neurons in hippocampal function is compelling.

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The dentate gyrus (DG) of the adult hippocampus is one of the two regions of the brain, together with the olfactory bulb, that produce large numbers of new neurons in mammals including humans [1]. The hippocampus has been associated with mainly two functions, the formation of memory [2] and the representation of space [3]. What is the importance of adult neurogenesis to hippocampal function? Two strategies have been primarily used to address this question: (1) to study the effect of modulation or ablation of adult neurogenesis on specific behaviors; (2) to study how particular behaviors activate adult-born neurons. In this review we focus on these two strategies and discuss important aspects related to the dynamics of the maturation of adult-born neurons and its relation to behavior.

1. Functional properties of developing DGCs are critical to their role in hippocampal function

The time required for maturation and functional integration of adult-born dentate granule cells (DGCs) is a critical determinant of their role in information processing. Newborn DGCs develop for several weeks to establish their functional properties, afferents and output connectivity [4–10]. That time is not fixed but depends on the species, since neuronal maturation occurs at a faster pace in rats than in mice [11]. In addition, the activity of the network surrounding newly generated DGCs could also influence their maturation. Different regions along the septotemporal axis of the hippocampus show different levels of activity and expression of immediate early genes (IEGs) [12]. Since local network activity can modulate neuronal maturation, the differential activation of the hippocampal network generates restricted domains where adult-born neurons mature at different rates [13].

By the end of this developmental process newborn DGCs become similar to those DGCs generated during perinatal development [14,15]. However, while developing, newborn cells display

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high input resistance, increased intrinsic excitability, and reduced GABAergic inhibition, physiological characteristics that are typical of immature neurons and make them functionally unique [4,6,16–18]. In mice, DGCs between 3 and 5 weeks of age produce action potentials in response to afferent stimulation [19], present higher levels of LTP [7] and are already connected with their postsynaptic targets [8]. The higher excitability and plasticity of immature DGCs opens the possibility that such neuronal population is mostly active in response to different stimuli in a less specific manner than mature DGCs.

2. Modulation of adult neurogenesis

The amount of neurogenesis in the DG can be importantly modulated by different factors that increase or decrease the number of newly generated DGCs that become incorporated in the circuit. It is now known that physical exercise or enriched environment increase DG neurogenesis [20–22], which is also the case for certain pathological conditions like ischemia [23] (see Table 1). On the other hand stress, aging and depression can decrease neurogenesis [24]. Some of the evidence on the role of adult neurogenesis in memory arises from experiments in which neurogenesis was increased by running and then the effects of that manipulation on learning performance were evaluated [21,25,26]. For example, running was initially shown to enhance spatial learning [21] and, more recently, it was found to exert an effect on DG-mediated pattern separation [25]. Moreover, exposing animals to an enriched environment increased neurogenesis and rendered an enhanced performance in spatial memory tests such as the Morris water maze (MWM) [27–30], in associative memory tests like instrumental conditioning [31] and also in novel object recognition tasks [32]. Interestingly, mutant mice lacking Toll-like receptor 3 (TLR3) exhibited increased neurogenesis and enhanced performance in the MWM, novel object recognition and contextual fear-conditioning tasks [33], highlighting again the relationship between DG neurogenesis and hippocampus-dependent memory performance.

Direct evidence that behavioral effects of exercise or enrichment are mediated by neurogenesis is scarce. Most studies discussed above establish a correlation between improved learning capabilities and exercise or enriched environment, conditions that are known to increase neurogenesis, but the requirement of neurogenesis is often not addressed. Enhanced learning may be due to increased neurogenesis, but it may also obey to factors other than neuronal production. As an example of the first case, enhanced novel object recognition after enrichment was abolished by antimitotic agents that block neurogenesis [32]. In contrast, other works have provided convincing evidence of improved hippocampus-dependent learning and behavior by enriched environment in the absence of neurogenesis [31,34].

Recent work has provided interesting insights about animals subjected to chronic social defeat stress. Even though it is known that stress reduces neurogenesis [35], some animals, the ones that displayed a persistent effect of stress reflected as social avoidance, exhibited increased neurogenesis presumably as a compensatory mechanism (perhaps "remembering" the stress). When neurogenesis was reduced by irradiation mice failed to display stress-induced avoidance [36]. This later experiment highlights the importance of the dynamics in the process under study. In particular the same stimulus, stress, can both decrease or increase neurogenesis and thus control behavioral output.

3. Ablation of adult neurogenesis

The most compelling evidence relating DG neurogenesis to learning and memory arises from ablation experiments. The question to be asked is: are there any alterations in learning and memory performance in animals lacking adult-born DGCs? Gathering consistent data on this fundamental question has been difficult due to the many variables involved. Those variables include animal species and strain, age of the ablated neurons, method of ablation, behavioral task and performance analysis. Thus, comparing behavioral studies from different laboratories is a complex task since there are no two studies in which most variables are the same. In mice, adult-born neurons require 3–5 weeks before they become functionally relevant to the hippocampal network (i.e. they respond to synaptic inputs, generate spikes and make synapses onto postsynaptic targets) [4,8,14,19]. This interval seems to be shorter in rats [11]. Therefore, the time between neurogenesis ablation and behavioral training defines the neuronal population that will be removed and to design meaningful experiments it should outlast the timing required for neuronal maturation. This has not always been the case [37–39]. In addition, three very different methods have been primarily used to abolish adult neurogenesis: irradiation, antimitotic agents and, more recently, inducible genetic ablations. Below we discuss the notion that the ablation method may greatly influence the outcome of behavioral experiments.

Spatial learning in the MWM and the Barnes maze, and associative learning such as contextual fear conditioning are the most commonly used tasks to assess the relevance of adult-born neurons in information processing in animals with ablated neurogenesis. Adult neurogenesis has also been involved in anxiety-related behaviors (recently revised by [40]). Analyzing spatial performance involves the ability to learn the task (acquisition period), remembering the task (short-term memory) and remembering after long delays (long-term memory). Analyzing all published data on ablation of adult neurogenesis in spatial learning shows that acquisition is impaired in some studies [41–44,46,47] whereas it is unaffected in others [39,45,48–52] (see Table 1) or even increased [53]. Interestingly, most studies do support an effect of abolished neurogenesis in either short- or long-term spatial memory [41,42,46,48,49,52], although some studies still show no effect [45,50,51].

The conflicting data on spatial learning cannot be accounted for by differences in species/strain. However, evidence seems to become more consistent when the ablation method is taken into account. Most experiments in which removal of adult neurogenesis was achieved by genetic manipulation (inducible transgenic animals or lentiviral transgene delivery) display impairment in spatial memory [41,42,44,46,48,49] (but also see [50,54]). The consistency of the inducible genetic approach might be due to the higher selectivity of the ablation, reduced degree of unspecific brain damage, and more appropriate control conditions (such as non-induced transgenic mice) compared to those of chemical antimitotic agents or irradiation.

Refining the protocols to evaluate qualitative aspects of spatial learning performance can also aid in dissecting the role of adult neurogenesis in hippocampal spatial processing. Detailed behavioral analysis in animals with ablated neurogenesis revealed impairment in learning strategies reflected as the inability to relocate a new position of a hidden platform when a previous position has been learned [43]. In addition, an impairment was observed in the ability to distinguish similar but not distinct spatial locations highlighting the role of adult neurogenesis in spatial discrimination [55].

The impact of adult neurogenesis has also been evaluated in associative memory tasks that depend on the hippocampus. Most experiments evaluating the effects of abolishing neurogenesis show substantial impairment in contextual fear conditioning. In this case, regardless on the method of choice, deficiencies are observed in both short-term [11,38,42,44,48,50,56–60] and long-term retention [56,60] (Table 1). However, there are some cases