



Review

Adult neurogenesis: Optimizing hippocampal function to suit the environment

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ARTICLE INFO

Article history:

Received 4 April 2011

Accepted 15 May 2011

Available online 23 May 2011

Keywords:

Adult neurogenesis

Reward

Stress

Learning

Anxiety

ABSTRACT

Numerous studies have attempted to determine the function of adult neurogenesis in the hippocampus using methods to deplete new neurons and examine changes in behaviors associated with this brain region. This approach has produced a set of findings that, although not entirely consistent, suggest new neurons are associated with improved learning and reduced anxiety. This paper attempts to synthesize some of these findings into a model that proposes adaptive significance to experience-dependent alterations in new neuron formation. We suggest that the modulation of adult neurogenesis, as well as of the microcircuitry associated with new neurons, by experience prepares the hippocampus to meet the specific demands of an environment that is predictably similar to one that existed previously. Reduced neurogenesis that occurs with persistent exposure to a high threat environment produces a hippocampus that is more likely to respond with behavior that maximizes the chance of survival. Conversely, enhanced neurogenesis that occurs with continual exposure to a rewarding environment leads to behavior that optimizes the chances of successful reproduction. The persistence of this form of plasticity throughout adulthood may provide the neural substrate for adaptive responding to both stable and dynamic environmental conditions.

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Since the rediscovery of adult neurogenesis in the mammalian hippocampus, focused attention has been on understanding the function of new neurons [1, for review see 2]. A growing number of studies using multiple methods to inhibit adult neurogenesis have assessed performance on tasks linked to the hippocampus [for review see 3]. These studies have produced results linking new neurons to learning and memory paradigms that require the hippocampus [4–11]. Unfortunately, these findings are sometimes inconsistent with one another and point to disparate roles for new neurons in cognitive function. For instance, some studies suggest that new neurons are important for context fear conditioning, spatial navigation learning [11] and pattern separation [12], while others do not [see 2,3 for reviews]. Notwithstanding inconsistencies in these findings, which may be due to differences in species, strains, methods of reducing adult neurogenesis and

learning paradigms, the overall picture seems to indicate that new neurons play a beneficial role in cognitive function. That is, in most cases (see [11,13] for exceptions), their removal is associated with impaired performance on cognitive tasks [6]. One possible approach to ascertaining a more general function for new neurons and determining their adaptive significance is to look at data from studies of new neuron inhibition in the context of information about what types of experience typically change the number of new neurons. These latter findings may provide clues about the environmental pressures that gave rise to and maintained adult neurogenesis throughout vertebrate evolution.

1. Experience and adult neurogenesis

Numerous studies have indicated that the production, differentiation and survival of new neurons are highly plastic processes that are regulated by experience. In general, experiences that are detrimental to well-being, such as exposure to physical or social stressors, reduce the production of new neurons in the dentate gyrus (see [2,14] for review). Similar effects have been observed

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with experimental increases in corticosterone levels in rodents suggesting that stress reduces adult neurogenesis by elevating glucocorticoid levels (see [14] for review). These findings are entirely consistent with the overall view that glucocorticoids are catabolic in nature and that growth inhibition is adaptive under conditions where survival may depend on shunting energy to systems that can be immediately useful to the organism. On the other hand, exposure to rewarding experience appears to enhance adult neurogenesis in the hippocampus (see [14]). Rewarding experiences as diverse as running [15], learning (under relatively low stress conditions) [16–18], sexual experience [19], living in an enriched environment [20] and intracranial self-stimulation [21] all increase the rate of adult neurogenesis in the dentate gyrus. Even short-term cocaine administration appears to have a stimulatory effect on adult neurogenesis [22] (although long-term cocaine administration has the opposite effect) [23]. The enhancing effects of rewarding experience on adult neurogenesis may seem surprising given the fact that each of these experiences produces a robust increase in circulating levels of glucocorticoids [24–28]. Taken together, these findings suggest that natural compensatory or buffering agents must exist in the brain to prevent the otherwise deleterious consequences of elevated glucocorticoids. Such a mechanism, or set of mechanisms, may suggest the importance of promoting neurogenesis in response to reward. Although the cues that enable this process remain incompletely explored, one possible factor is the neuropeptide oxytocin. Oxytocin is released in rewarding social situations (see [29] for review), may play an important role in prosocial behavior (see [30] for review) and has recently been shown to stimulate adult neurogenesis in the dentate gyrus [31].

Why would changes in neuronal growth be so different under aversive versus rewarding environmental conditions? The

dichotomous response of adult neurogenesis to two different types of conditions may indicate that new neurons provide a mechanism for shaping the hippocampus to more effectively cope with the environment in the future. That is, aversive and potentially threatening life conditions may provide the animal with more effective means to deal with similar experiences in the future in part by reducing the pool of available new neurons. Conversely, rewarding life experiences may enable the animal to maximize future opportunities under beneficial environmental conditions by increasing the pool of available new neurons. Support for this idea would be evidence that reduced numbers of new neurons are associated with behaviors that insure survival under aversive conditions and that increased numbers of new neurons are associated with behaviors that maximize chances for reproduction. The remainder of this paper will explore this model further by evaluating both supportive and contradictory evidence.

2. New neurons as substrate for fine-tuning behavioral responses to the environment

If it is a reasonable assumption that past experience is predictive of the future, then animals exposed to chronic aversive experiences are likely to encounter more such experiences in the future unless their living conditions change drastically. In the wild, living under conditions of chronic stress may be the result of social position, e.g., being a subordinate in a dominance hierarchy, or environmental conditions, e.g., harsh climate, limited food and/or many predators. Stress-induced reduction in adult neurogenesis may encourage an animal to respond more cautiously in the future, to explore less and display more anxiety-like behavior (Fig. 1). Such an outcome may increase the likelihood of the animal's survival, especially if

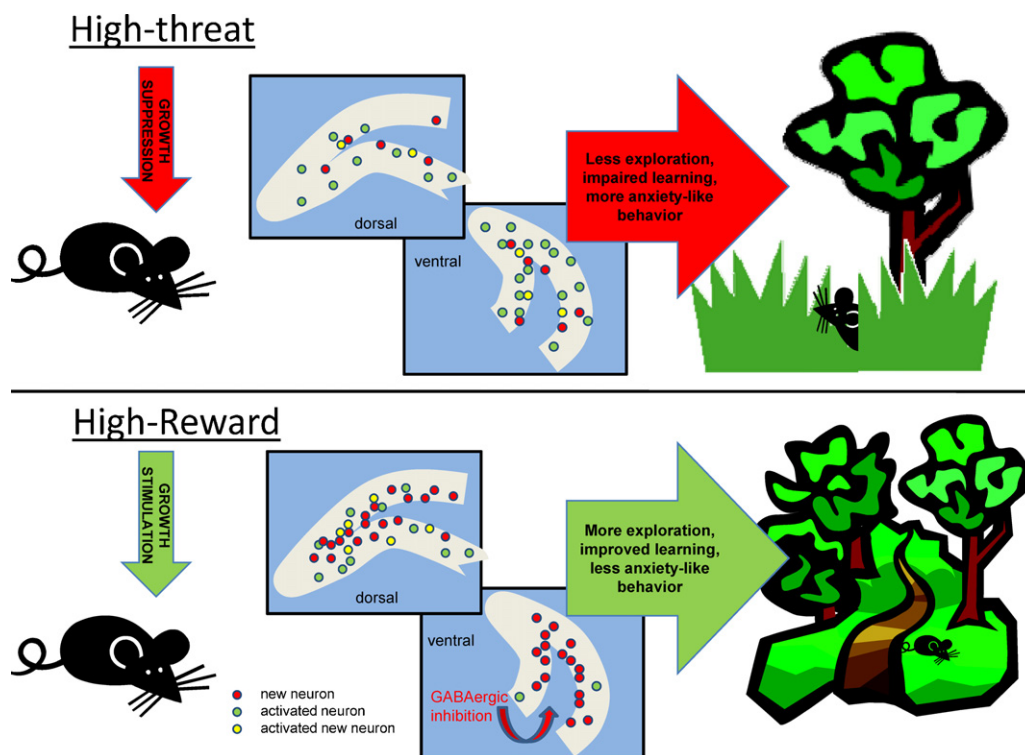


Fig. 1. Schematic diagram of a proposed model of how different environments dominated by negative or positive emotional valence lead to changes in adult neurogenesis and associated microcircuitry that produce more adaptive behavioral responses. Top: Animals living in a high-threat environment will show a decrease in adult neurogenesis in both the dorsal and ventral dentate gyrus. This decrease in adult neurogenesis would produce a reduction in exploration and an increase in anxiety-like behavior. Such behavioral responses are likely to maximize the chances of survival. Bottom: Animals living in a high-reward environment will show an increase in adult neurogenesis in both the dorsal and ventral dentate gyrus. The increase in new neurons is likely to facilitate exploration and learning, particularly under low-stress conditions. Persistent high-reward experiences are also likely to produce changes in the dentate gyrus microcircuitry such that high stress would more readily engage GABA inhibitory mechanisms in the service of dampening activity in the ventral dentate gyrus, thus producing reduced anxiety-like behavior.

aversive and potentially dangerous experiences can be minimized or avoided altogether by less exploratory behavior. The available evidence on chronic stress and anxiety-like behavior is consistent with this possibility – chronic stress produces an increase in anxiety-like behavior [32–34]. Here it is worth noting that the most commonly used tests of anxiety for rodents (elevated plus maze, open field) consider reduced exploration as a measure of anxiety [35].

Again assuming that past experience has some predictive value, animals exposed to repeated rewarding experiences are likely to encounter more such experiences in the future unless their environment changes drastically. Living under conditions of repeated reward may be dictated either by the social structure, e.g., being dominant in a dominance hierarchy, or by characteristics of the overall physical environment, e.g., mild climate, abundant palatable food and/or few, if any, predators. Naturalistic rewarding experiences such as sexual behavior, eating and unforced physical activity, require voluntary engagement in certain behaviors, an outcome that is more likely to occur in animals displaying more exploration. Since most naturalistic rewarding experiences increase the likelihood of successful reproduction, a drive to engage in these behaviors seems adaptive. Rewarding experience-induced increases in adult neurogenesis may encourage exploratory behavior in part by reducing anxiety-like responses. Here again, the available evidence on rewarding experience and anxiety is consistent with this possibility – rewarding experience reduces anxiety-like behavior [19,36–39]. Furthermore, rewarding experience has been associated with improved performance on cognitive tasks that require the hippocampus, including tasks that involve navigation and novelty under low stress conditions, such as spatial navigation learning and object recognition [40–42]. Taken together, these findings support a model in which reward-induced increases in new neurons facilitate exploration and learning so that responses to such experiences in the future will be maximized. Conversely, stress-induced decreases in new neurons may limit exploration in the service of survival while coincidentally diminishing performance on certain types of learning tasks. Although these scenarios seem plausible, they are overly simplistic when considered in the context of what we know about the role of the hippocampus in anxiety regulation.

3. Dorsal versus ventral hippocampus

Lesion and electrical stimulation studies suggest that the hippocampus plays an anxiogenic role [43–47]. As mentioned above, experiences that increase adult neurogenesis, such as running and sexual experience, are associated with a reduction in anxiety [19,36–39]. Since new neurons are excitatory and exhibit enhanced synaptic plasticity [48], it is difficult to reconcile these two sets of findings. In the simplest interpretation, more new excitatory neurons should work like electrical stimulation of the ventral hippocampus to produce an anxiogenic response. Instead, the opposite is the case – more new neurons are associated with an anxiolytic response. In most instances, the increase in new neurons occurs throughout the dentate gyrus – in some cases, it is localized to the ventral dentate gyrus [31] and yet, anxiety-like behavior decreases.

There are many possible reasons for this paradox. First, new neurons themselves may alter patterns of activity in the ventral hippocampus that convey an anxiolytic response. In this regard, it may be relevant that coordinated theta activity in ventral hippocampus and medial prefrontal cortex is correlated positively with anxiety-like behavior [49]. The extent to which new neurons in the ventral hippocampus might interfere with coordinated theta activity, however, remains unknown although evidence from anesthetized rats suggests that new neurons may interfere with

synchronized activity in the dentate gyrus [50]. Second, increased numbers of new neurons in the dorsal hippocampus may somehow dominate the behavioral output of the ventral hippocampus. Since dorsal and ventral hippocampus do not communicate extensively with one another [51], such an effect would likely be indirect. Third, new neurons produced under conditions of reward may be specially organized so that they can differentially respond to low and high stress conditions. That is, new neurons produced under rewarding circumstances may be wired differently than those produced under baseline or high stress conditions. This differential wiring in animals with a history of high reward may enable the flexible switching from activation of relatively large numbers of new excitatory neurons under low stress conditions in the service of facilitated learning and exploration, to inactivation of new neurons under high stress conditions in the service of dampening anxiety-like responses. This may be accomplished by changes in the degree to which inhibitory mechanisms in the dentate gyrus are engaged under different situations. Thus, rewarding experiences may alter stress-induced inhibitory tone of the dentate gyrus, which may allow for more flexible neuronal activity in response to different environmental cues. Although the specifics of such a proposal remain unknown, our preliminary data suggest that the granule cells of the dentate gyrus in animals exposed to long term rewarding experience exhibit less stress-induced activation presumably because inhibitory interneurons that project to granule cells become engaged [52].

In a similar regard, it is relevant to note that physical activity alters GABA-A subunits in the dentate gyrus [53] and increases the expression of parvalbumin in inhibitory basket cells in the dentate gyrus [54]. Basket cells synapse directly on granule cells and exert a powerful inhibitory action on this population [51]. Environmental enrichment has also been shown to increase GABA expression in the hippocampus ([55], for review see [56]). Given these findings, it is possible that the hippocampus of animals living under conditions of high reward becomes organized to minimize the impact of high-stress threatening conditions by enhancing stress-induced GABAergic inhibition. In such stressful circumstances, then, increased numbers of new neurons are irrelevant to the behavioral response since those cells would be silenced. The beneficial actions of new neurons in animals with a high reward history would come into play only under circumstances of low stress when learning opportunities exist. In this scenario, activation of a larger pool of immature neurons would provide a substrate for facilitating exploration and learning. The advantage of having more new activated neurons under low stress conditions would be absent in animals with a history of high-threat experiences because of suppressed neurogenesis (Fig. 1). Under high stress conditions, animals with a high-threat history would lack any substantial stress-induced GABAergic inhibition of granule cells in the ventral dentate gyrus, leading to more anxiety-like behavior.

Ongoing structural plasticity in the adult brain presents a potential mechanism or set of mechanisms by which the brain can modify itself so that behavior is better suited to the environment. Changes in the number of new neurons, and in the microcircuitry that determines their activation, as a result of a prolonged set of similarly valenced experiences may encourage behaviors that are most likely to promote reproduction or survival given the likelihood that environmental conditions will persist for some duration of time. In the event that environmental conditions change substantially, the continued ability to modulate new neuron production and hippocampal microcircuitry would also allow for the modification of behavioral responses throughout adulthood. Although much experimentation is needed to identify mechanisms by which reward enhances learning and reduces anxiety, the proposed model provides an adaptive framework for generating specific hypotheses about reward, new neurons, hippocampal circuitry and behavior.

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