The beneficial effects of physical activity on impaired adult neurogenesis and cognitive performance

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Neurogenesis occurs in two neurogenic zones in the adult brain: new neurons are born at the subventricular zone of the lateral ventricles and then migrate to the olfactory bulb, and at the subgranular zone to integrate the granular cell layer of the dentate gyrus. The hippocampus is involved in learning and memory and the generation of new hippocampal neurons has been suggested to be a new form of plasticity implicated in these processes. In the last decades, diverse intrinsic and epigenetic factors have been identified to influence adult neurogenesis but the underlying mechanisms remain unclear. In a recent study, Lafenetre et al. (2010) showed the beneficial influence of physical voluntary activity on adult neurogenesis and cognitive performance in a transgenic mouse, the synRas mouse via brain-derived neurotrophic factor. Here we review how hippocampal neurogenesis can be regulated by environmental factors and the possible role of the newly generated cells in learning and memory.

Keywords: Ras, exercise, BDNF, object recognition, learning, memory

INTRODUCTION

Altman and Das (1965) proposed in 1965 the revolutionary idea that new neurons are born in the adult brain. For decades, the concept has been ignored until it was rediscovered in the early 1990s. It is now well accepted that new neurons are born throughout life, even in humans (Eriksson et al., 1998; Jin et al., 2004; D’Alessio et al., 2010) and in aged animals (Kuhn et al., 1996; Kempermann et al., 1998a). Adult neurogenesis has been clearly demonstrated and confirmed in two brain regions: the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus (DG) of the hippocampal formation (Kempermann and Gage, 1999). Cells born in the adult SVZ migrate through the rostral migratory stream and become granule neurons and periglomerular neurons in the olfactory bulb. Cells born in the adult SGZ migrate into the granule cell layer of the DG and become dentate granule cells (DGC).

It is only in the last decade that hippocampal adult neurogenesis has become a hot topic. Many studies have been designed to characterize these newly generated neuronal cells (Kempermann et al., 2004; Zhao et al., 2006), to unravel the regulation of the different maturation stages (Zhao et al., 2008) and to unveil the potential meaning of this phenomenon (Zhao et al., 2008; Deng et al., 2010).

The newly generated cells undergo different maturation stages to become functional mature neurons. As a consequence of neurons being born in a continuous manner, the DG is composed of a heterogeneous population of dividing and non-dividing, immature and mature, neuronal and non-neuronal cells. It has thus been difficult to understand the progression of these developmental
Adult neurogenesis

Generation of new neurons in the adult brain throughout life in a multi-step process including the proliferation of the neural progenitor cells, the fate determination, the differentiation and the migration, the morphogenesis and the maturation of the neuronal cells and the integration into the neuronal network.

Neurotrophins

Neurotrophins are proteins that are capable of signaling particular cells in an autocrine or paracrine manner to proliferate, survive, differentiate, or grow. There are four neurotrophins: nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4 (NT-4). They can activate the Ras/MAPK signaling cascade by binding to specific tropomyosin-receptor-kinase receptors with preferential affinities: NGF to TrkA, BDNF and NT-4 to TrkB, NT-3 to TrkC. They can also bind to the p75 neurotrophin receptor.

Epigenetics

Epigenetics, as opposed to genetics, studies the interplay between environment and genes, in particular the regulation of gene expression, which results in a given phenotype. In adult neurogenesis, intrinsic and extrinsic factors alter the pattern of DNA methylation within the dentate gyrus (Covic et al., 2010). In this review, we consider environmental factors and experience as extrinsic epigenetic factors.

Steps. Many studies have first examined the expression of diverse cell markers. Kempermann et al. (2004) have developed a model of six developmental milestones of hippocampal adult neurogenesis based on their basic morphology and the combinatorial expression of six fairly stage-specific markers. Type-1 cells are the putative stem cells. They are characterized by their radial process extending to the inner molecular layer where they ramify, and by the expression of both nestin and glial fibrillary acidic protein (GFAP). Nestin-positive cells that do not express GFAP nor doublecortin are classified as type-2a putative progenitor cells. Doublecortin is indeed expressed in type-2b, type-3 cells, both putative progenitor cells, and by immature granule cells. Type-2b cells display an irregularly shaped dense nucleus and the coexpression of nestin. Type-3 cells have a rounded nucleus and do not express nestin nor GFAP. Postmitotic immature neurons are further characterized by the emergence of dendrites and the coexpression of calretinin or NeuN. Finally, mature DGC have developed a dendritic arborization and are calbindin- and NeuN-positive. Recent studies have suggested that the electrophysiological and morphological properties of the newborn cells gradually emerge during neuronal maturation. These properties are needed by the young neurons for successful integration into the existing synaptic circuits (Zhao et al., 2006, 2008; Aimone et al., 2010).

The hippocampus is undisputedly one of the brain centers essential for learning and memory. The idea that new neurons are needed to build new memories has been quick to emerge. However, easily generated ideas are often difficult to prove. The concept implies hippocampal adult neurogenesis as being a new form of structural plasticity correlated to the processes of synaptic learning and memory formation. Should this be the case, animals with impaired neurogenesis should, compared to wildtype animals, show alterations in acquisition, retention, recall or extinction of some kinds of information like spatial or contextual information.

Lafenetre et al. (2010) have used the syn-Ras transgenic mouse model in order to better understand the role of adult neurogenesis in learning and memory. The mouse has a synapsin1 promoter-driven overexpression of the constitutively activated G-protein p21Ras in neurons. Intriguingly, this mouse has significantly depressed rates of hippocampal adult neurogenesis, and this is associated with impaired performance in an object recognition task (Lafenetre et al., 2010). Both, impaired neurogenesis and impaired object recognition could however be rescued by exposing synRas mice to free access to a running wheel (Lafenetre et al., 2010; Table 1).

Here we review the study by Lafenetre et al. (2010), starting by presenting the regulation of adult neurogenesis by physical activity as an epigenetic factor and the possible implication of neurotrophins as molecular mediators. We will finally discuss the relationships between adult neurogenesis and learning and memory.

EPIGENETIC REGULATION OF ADULT NEUROGENESIS

Adult neurogenesis has been shown to be a dynamic process that can be regulated both positively and negatively by many factors, including epigenetic factors. Indeed, in the last decades, five of them have clearly been identified and studied. Whereas stress and aging downregulate adult neurogenesis, physical activity, environmental enrichment, and learning and memory have beneficial effects (Figure 1).

Physical activity is the environmental factor that has been selected by Lafenetre et al. (2010) to rescue the reduced adult neurogenesis of the syn-Ras mice due to reduced proliferation. Voluntary physical activity is indeed the most potent enhancer of adult proliferation (van Praag et al., 1999a; Olson et al., 2006; Fabel and Kempermann, 2008). The increase in neurogenesis is however region-specific and occurs only in the hippocampus and does not stimulate the olfactory bulb neurogenesis (Brown et al., 2003).

| Proliferation (number of BrdU-labeled cells) | BDNF levels | Dendritic arborization of immature neurons | Object recognition performance |
|---------------------------------------------|-------------|-------------------------------------------|-----------------------------|
| Genotypes                                  | WT          | synRas                                   | WT                          | synRas                      |
| Basal conditions                           | ++          | +                                        | ++                          | +                           |
| Running conditions                         | +++         | +++                                      | ++                          | ++                          |

Proliferation, assessed by the number of bromodeoxyuridine (BrdU)-labeled cells, brain-derived neurotrophic factor levels, dendritic arborization of doublecortin-labeled cells and object recognition performance have been studied in wildtype (WT) and transgenic (synRas) mice under basal conditions and with free access to a running wheel. Physical activity rescues the reduced adult hippocampal neurogenesis and the recognition memory impairment.

Table 1 | Main results at a glance (Lafenetre et al., 2010).

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In order to study the influence of physical activity in rodents, a running wheel is usually introduced in their home cage. However, the modalities could vary from one experiment to another and could induce differential effects. First, the access to the wheel could be free or restricted to some hours per day or night (Holmes et al., 2004). Second, running is limited to physical activity when rodents are housed individually but could also be considered as a social activity when the animals are housed per group. Indeed, when rodents are isolated, the effects may be delayed or prevented (Stranahan et al., 2006; Leasure and Decker, 2009) but this is still under debate (Kannangara et al., 2009, 2010). Thirdly, grouped animals could use the running wheel according to two modes: some are very “active” and seem to become addicted to running whereas other individuals are “passive users.” In the study by Lafenetre et al. (2010), grouped mice had free access to the running wheel: this paradigm gave the greatest opportunity to enhance adult neurogenesis.

Lafenetre et al. (2010) have thus confirmed the positive regulation of adult neurogenesis by physical activity that had been described earlier in wild type rodents (van Praag et al., 1999a,b; Fabel et al., 2003; Farmer et al., 2004). This paradigm is also efficient in stimulating the neurogenesis of synRas mice characterized by a reduced basal adult neurogenesis in the hippocampus (Figure 2; Lafenetre et al., 2010; Manns et al., 2010) to an extent comparable to that in wildtype animals. The ways by which physical activity promotes proliferation must thus differ from the regulation of proliferation in basal conditions (Lafenetre et al., 2010). It has earlier been shown that neurogenesis could be partially rescued in aged animals by voluntary physical activity. This also suggests the regulatory mechanisms could be modified during aging but that the cells could still respond to external stimuli (van Praag et al., 2005; Kronenberg et al., 2006).

Wheel running has also been shown to improve hippocampal-dependent spatial learning in rodents in the Morris water maze (Fordyce and Farrar, 1991; van Praag et al., 1999a; Vaynman et al., 2004) and in the radial maze (Anderson et al., 2000). Other tasks like contextual fear conditioning have also been used to show the running-induced improvement in cognitive performance (Baruch et al., 2004).

The beneficial effect of physical activity could be mediated by increased synaptic plasticity (van Praag et al., 1999b; Farmer et al., 2004), neurotransmission and growth factor expression.
(Cotman and Berchtold, 2002) that are observed both in running mice and rats. In their study, Lafenetre et al., (2010) have focused on the involvement of brain-derived neurotrophic factor (BDNF) as one of the potential mediators of these effects.

**NEUROTROPHINS AND ADULT NEUROGENESIS**

Brain-derived neurotrophic factor is a neurotrophin that is highly expressed in the hippocampus and has been implicated in synaptic plasticity and neuronal development (Binder and Scharfman, 2004). BDNF is known for its survival-promoting effects on new neuroblasts through the TrkB receptor (Bath et al., 2008). Environmental factors like environmental enrichment and physical activity induce an increase in BDNF expression level even after a short exposure to a running wheel (Cotman and Berchtold, 2002). Moreover, running wheel activity increases the levels of the phosphorylated form of the BDNF receptor TrkB (Vaynman et al., 2003).

The functional role of BDNF in the regulation of the hippocampal adult neurogenesis is quite controversial. Lafenetre et al. (2010) showed a running-induced increase in BDNF protein level that was associated with increased level of bromodeoxyuridine (BrdU)-labeled cells and doublecortin-labeled cells in both wildtype and synRas mice. BDNF acts through the TrkB receptor which is present on doublecortin-expressing cells (Donovan et al., 2008; Lafenetre et al., 2010). The authors thus suggested that BDNF could not only promote the proliferation of doublecortin-expressing neuronal precursor cells but also stimulate the dendritic arborization of the immature neurons and facilitate their survival (Figure 3).

The infusion of BDNF for 2 weeks directly into the hippocampus increases neurogenesis of granule cells (Scharfman et al., 2005). However, classical genetic studies manipulating directly the expression of BDNF do not lead to such clear results. Indeed, enhanced and reduced cell proliferation in heterogeneous BDNF knockout (BDNF+/−) mice have been reported (Lee et al., 2002; Sairanen et al., 2005). The survival rate of the neurons must however be dependent on BDNF expression as impaired levels of cell survival were observed in both studies (Lee et al., 2002; Sairanen et al., 2005). Moreover, enriched environment does not enhance the survival of newborn cells in BDNF+/− heterogenous knockout mice (Rossi et al., 2006).

In accordance with the role of BDNF in promoting the dendritic differentiation of mature neurons (McAllister et al., 1996; Wirth et al., 2003), the dendritic arborization of the DGC is more developed in BDNF-overexpressing transgenic mice (Tolwani et al., 2002). In a recent study, the role of BDNF in different stages of adult neurogenesis has been assessed in conditional knockout mice that lack the expression of BDNF in mature neurons of the adult hippocampus, resulting in 50% of the BDNF levels. BDNF has been suggested to play a critical role in the regulation of the survival and of the dendritic development of neuronal precursor cells but seems less important for exercise-induced proliferation of the cells (Choi et al., 2009). The conditional deletion of the TrkB receptor in progenitor cells leads to impaired basic organization of synaptic connections and compromises the survival and the integration of the newborn neurons (Bergami et al., 2008). Thus, whereas the role of BDNF in the proliferation of neuronal progenitor cells is still unclear, the survival and the integration of these newborn neurons rely on the good functioning of BDNF/TrkB signaling.

Due to the cellular heterogeneity of the DG, the understanding of the role of BDNF and other growth and neurotrophic factors, like VEGF, IGF1, Erythropoietin, remains difficult. Presumably, they have to be tightly regulated and can act differentially on different developmental stages of the various cellular subsets.

**ADULT NEUROGENESIS AND LEARNING AND MEMORY**

What is adult neurogenesis good for? The functionality of the newly generated neurons has remained incompletely understood. With regard to the well-characterized role of the hippocampus in learning and memory, hippocampal adult neurogenesis has been proposed to be a new form of plasticity that underlies these processes.

Three technical approaches have been used to study the involvement of the newly generated neurons in learning and memory processes: the neural progenitor cells are ablated by pharmacological treatment, by irradiation or by genetic tools. Neural progenitor cells are indeed more vulnerable than mature granule cells. Injections of the DNA methylating agents, methylazoxymethanol (MAM), or more recently of Temozolomide (TMZ), significantly reduce the rate of adult neurogenesis. X-ray irradiation has also been a very powerful, even stronger, tool. However, these techniques may induce side-effects that could cause other detrimental effects on brain physiology and function (Bruel-Jungerman et al., 2007). With the generation of new genetic tools, it has been possible to specifically target the neural progenitor cells in the hippocampus and better
assess the role of the new neurons in learning and memory processes.

Besides, the use of other transgenic mice has helped in the better characterization of some molecules that could be involved in the regulation of adult neurogenesis. As in Lafenetre et al., (2010), many studies have used environmental stimuli that could affect both, the animals’ behavior and adult neurogenesis (Figure 3).

Deng et al. (2010) have recently reviewed the different behavioral tasks that have been performed with animals subjected to an ablation of progenitor cells. Controversial results have been obtained using similar experimental paradigms. For instance, the involvement of adult neurogenesis in the acquisition of the Morris water maze test, the most commonly used paradigm to test hippocampal functions, has been reported by Dupret et al. (2008), Farioli-Vecchioli et al. (2008), Garthe et al. (2009), and Zhang et al. (2008). By contrast, other studies have reported that adult neurogenesis is not required for the acquisition of the Morris water maze test (Shors et al., 2002; Madsen et al., 2003; Raber et al., 2004; Rola et al., 2004; Snyder et al., 2005; Deng et al., 2009; Jessberger et al., 2009). Similarly, is adult neurogenesis necessary for long-term retention of the location of the hidden platform? When progenitor cells are ablated by irradiation (rat; Snyder et al., 2005), viral disruption of the Wnt signaling (rat; Jessberger et al., 2009) and genetic disruption (mouse; Dupret et al., 2008; Farioli-Vecchioli et al., 2008; Zhang et al., 2008), performances are impaired. However, the retention is only affected 1 week after the viral injection in the genetic model of Deng et al., (2009) and only the retention of the reversal is affected by TMZ treatment (Garthe et al., 2009). Other studies have not found any positive correlation between reduced adult neurogenesis and impaired cognitive performance in the Morris water maze (Shors et al., 2002; Mashi et al., 2006; Saxe et al., 2006) and it has even been revealed that inhibiting adult neurogenesis could lead to better learning and memory performances (Kerr et al., 2010).

Similar contradictory results have been obtained in the contextual fear conditioning paradigm which is also a key test to assess the role of the hippocampus. Some studies have found deficits in freezing behavior (Saxe et al., 2006; Wincur et al., 2006; Imayoshi et al., 2008; Warner-Schmidt et al., 2008; Hernandez-Rabaza et al., 2009; Snyder et al., 2009) but no effect on freezing were reporting by others (Dupret et al., 2008; Zhang et al., 2008; Snyder et al., 2009). While specific effects on the formation but not the extinction of contextual fear memory have been found in strongly irradiated mice, mice that have received MAM injections (Ko et al., 2009) or mice that have been irradiated to a lesser extent (Kitamura et al., 2009; Ko et al., 2009) are not impaired. By contrast, in Nestin-tk mice with ablation of actively dividing progenitor cells by ganciclovir, impairment in freezing or fear conditioning is not observed, yet they are not able to extinguish their fear response to the context as efficiently as the wildtype mice (Deng et al., 2009).

Lafenetre et al. (2010) have proposed that the newly generated neurons are important for object recognition. The synRas mouse has a reduced adult neurogenesis and is impaired in exploring and discriminating a novel object compared to a familiar object. However, stimulating adult neurogenesis by physical activity rescues these deficits (Table 1). Similar deficits have been observed in rats that have been injected with a lentiviral virus targeting the Wnt signaling (Jessberger et al., 2009). However, irradiation does not lead to comparable deficits (Madsen et al., 2003; Rola et al., 2004; Clelland et al., 2009). Several other studies employing hippocampus-dependent or independent tasks have also led to inconclusive results (see Deng et al., 2010 for review).

Such discrepancies could reflect the importance of many factors. For instance, species and strain/substrain differences of brain endophenotype are crucial. Recent studies have shown how dramatic hippocampal activity varies between standard laboratory mouse lines including those used for genetic engineering. Electrical activity of neuronal networks is a driving force, e.g., for the production, release and action of BDNF, the structural differentiation of neurons and the
Pattern separation
Process allocated to the dentate gyrus that renders the output firing patterns in a network less similar than the input firing patterns, either with neurons firing at different rates or with a different set of neurons. This would help avoiding interferences between memories to be encoded by the CA regions of the hippocampus.

ability to form meaningful circuits. In particular, mouse lines differ in the patterns of spontaneous and evoked gamma oscillations, which are considered to be central to cognitive performance (Jansen et al., 2009). Strains also differ in the rates of proliferation and/or survival of newly formed cells (Kempermann and Gage, 2002) and this correlates with deficits in learning tasks (Kempermann et al., 1998b). Even substrains of the frequently used C57 strain differ dramatically in many behavioral aspects (Siegmund et al., 2005; Matsuo et al., 2010). The different ablation protocols may also affect different populations of cells that would be more vulnerable according to their maturation stage (Deng et al., 2010). Equally important are the collateral side-effects, the parameters used to assess the different phenotypes, the cognitive demand of the test, age, sex, and presumably the life history of the individual animals. It is thus difficult to integrate the results of different studies with so many variables. It would thus be needed to standardize protocols to target stage-specific cells in specific conditions.

An often overlooked aspect is that most experimental paradigms are primarily designed to assess the role of the hippocampus with all its input, intrinsic, and output networks. Are the tests adequate for understanding the role of the newly generated granule cells in the DG? Of course, the DG is considered as the information gateway to the hippocampus and has been specifically shown to be involved in pattern separation (Gilbert et al., 2001; McHugh et al., 2007). Computational models based on this function of the DG have been proposed for explaining either the addition of the new neurons in the network or the replacement of old DGC by these new neurons (Aimone et al., 2009, 2010; Deng et al., 2010). New born cells would thus help avoiding interferences between new and already established memories and promoting the individuals’ behavioral adaptation. Studies directly assessing this role are thus needed to better understand the real involvement of adult neurogenesis in learning and memory processes. According to a recent study, the newly generated cells in the DG must have a functional implication in pattern separation only when stimuli are presented with little separation in space, but not when they are widely separated (Clelland et al., 2009). Similarly, voluntary running improves the performance of the subtle discrimination of the location of two adjacent identical stimuli, which is tightly correlated to adult neurogenesis (Creer et al., 2010). Adult new neurons may thus be important for pattern separation and for encoding fine spatial distinctions (Clelland et al., 2009; Creer et al., 2010).

CONCLUSION
Lafenetre et al., (2010) have been able to show that voluntary physical activity could rescue two main phenotypes, the reduced adult neurogenesis and the impaired performance in an object recognition test, of a genetically modified mouse via an increase of BDNF. These results thus support the idea that adult neurogenesis is a dynamic process that is under the influence of environmental changes and that this form of plasticity is regulated by neurotrophic factors like BDNF.

Epigenetic factors, physical activity, enriched environment, aging, stress, and learning induce changes in both, the rate of adult neurogenesis and the behavior of the individual. It thus appears straight forward to associate both phenomena. However, the causal relationships are still not clearly determined and the role of adult neurogenesis in learning and memory processes remain obscure due to the many discrepant results. More studies are needed to better determine the effects of the various extrinsic factors on the progenitors and the subsequent stages of differentiation of the newly generated neurons, and their ability to integrate into the adult DG. Furthermore, the functional involvement of the newly generated granule cells must be further studied in the restricted context of the direct role of the DG. Computational models will thus help in elaborating theories that could be tested with animal models.

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