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# Role of Adult Hippocampal Neurogenesis in Cognition in Physiology and Disease: Pharmacological Targets and Biomarkers

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## Abstract

Adult hippocampal neurogenesis is a remarkable form of brain structural plasticity by which new functional neurons are generated from adult neural stem cells/precursors. Although the precise role of this process remains elusive, adult hippocampal neurogenesis is important for learning and memory and it is affected in disease conditions associated with cognitive impairment, depression, and anxiety. Immature neurons in the adult brain exhibit an enhanced structural and synaptic plasticity during their maturation representing a unique population of neurons to mediate specific hippocampal function. Compelling preclinical evidence suggests that hippocampal neurogenesis is modulated by a broad range of physiological stimuli which are relevant in cognitive and emotional states. Moreover, multiple pharmacological interventions targeting cognition modulate adult hippocampal neurogenesis. In addition, recent genetic approaches have shown that promoting neurogenesis can positively modulate cognition associated with both physiology and disease. Thus the discovery of signaling pathways that enhance adult neurogenesis may lead to therapeutic strategies for improving memory loss due to aging or disease. This chapter endeavors to review the literature in the field, with particular focus on (1) the role of hippocampal neurogenesis in cognition in physiology and disease; (2) extrinsic and intrinsic signals that modulate hippocampal neurogenesis with a focus on pharmacological targets; and (3) efforts toward novel strategies pharmacologically targeting neurogenesis and identification of biomarkers of human neurogenesis.

## Keywords

Adult neurogenesis • Neural stem cell • Hippocampus • Cognition

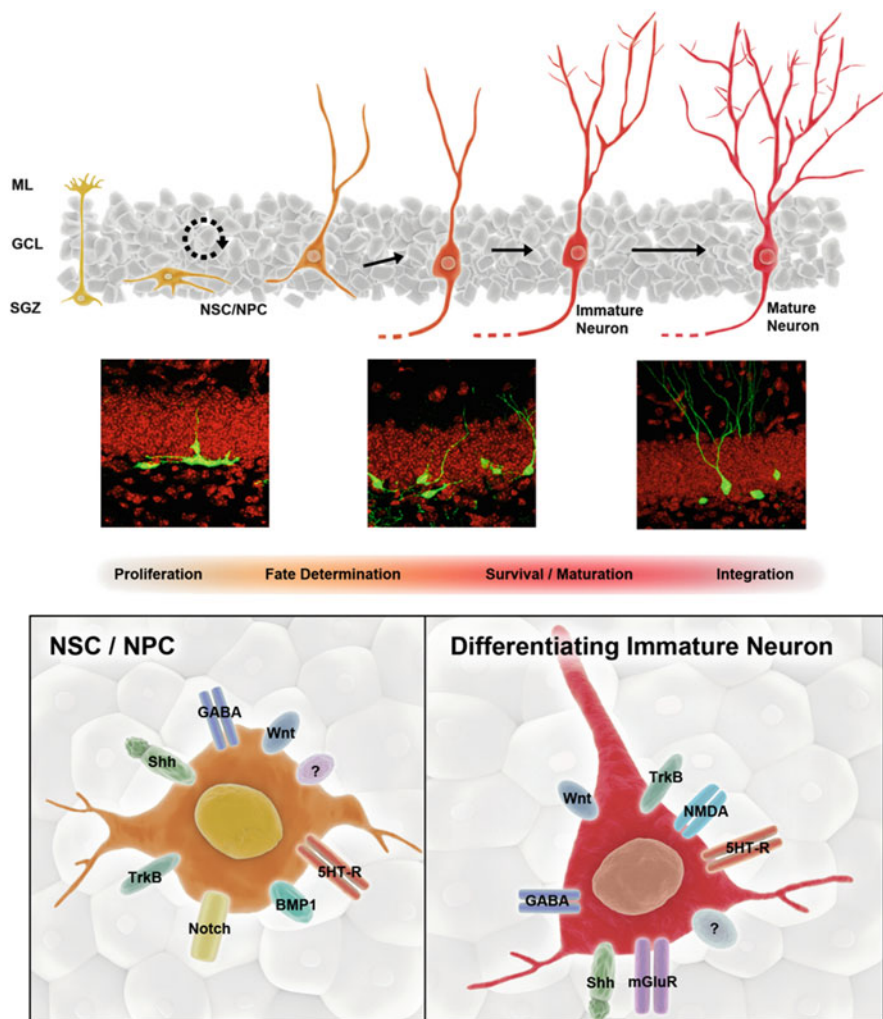
## 1 Introduction: Adult Hippocampal Neurogenesis

Purification of prospective neural progenitor cells, which are characterized by their potential to proliferate and give rise to differentiated neural progeny *in vitro*, has been successfully achieved from many regions of the adult mammalian central nervous system (CNS). However, despite the widespread distribution of neural precursors throughout the adult brain, adult neurogenesis is maintained in only

two discrete regions of the adult mammalian brain: the subventricular zone of the lateral ventricles (Altman 1969; Lois and Alvarez-Buylla 1994; Alvarez-Buylla and Garcia-Verdugo 2002) and the subgranular zone of the dentate gyrus of the hippocampal formation (Kaplan and Hinds 1977; Cameron et al. 1993).

From a neuroscientific perspective, hippocampal adult neurogenesis is of major interest as (1) the generation of new hippocampal neurons contributes to hippocampal function including learning and memory and mood regulation; (2) hippocampal neurogenesis is involved in the pathophysiology of depression, schizophrenia, age-related memory impairment, and multiple neuronal developmental disorders including autism spectrum disorder; and (3) the process of developing newborn neurons in a mainly restrictive environment as the adult brain provides an *in vivo* model to elucidate the molecular and cellular basis of neural regeneration which ultimately could be harnessed to develop novel therapies for neurodegenerative diseases.

The process of generating new granule neurons from adult neural stem cells is a highly dynamic process and at the same time tightly regulated at multiple developmental stages. Developmental stages include neuronal precursors cell proliferation, differentiation, survival, migration, and integration into preexisting hippocampal networks (see Fig. 1). Hippocampal neural stem cells, commonly referred to as radial Type I cells, have the capacity to self-renew and to differentiate into neurons and astroglia (Bonaguidi et al. 2011; Encinas et al. 2011; Lugert et al. 2010). They are localized in the subgranular zone of the dentate gyrus (DG) with a characteristic radial process spanning through the molecular layer and express the radial-glia marker GFAP (Seri et al. 2001; Kriegstein and Alvarez-Buylla 2009). Active Type I cells give rise to transient amplifying neural precursor cells (NPC), referred to as Type II cells, which then develop into mature granule neurons unless negatively selected by hippocampus resident microglia (Sierra et al. 2010). Morphological maturation of newborn granule neurons includes the development of dendritic trees into the molecular cell layer of the dentate gyrus (DG) and the projection of axons toward CA3 to become functionally integrated (Hastings and Gould 1999; Toni et al. 2007). During development, newly generated cells are characterized by a temporally ordered expression of stage-specific markers and changes in morphological and functional properties. From a morphological standpoint, differentiating progenitors located in the subgranular zone show bipolar horizontal processes; after cell cycle exit they develop the primary apical dendrite toward the molecular cell layer and axons toward the CA3 region and show progressive increase in the complexity of the dendritic tree during maturation. Morphological changes are paralleled by dynamic expression of specific marker proteins. Early in the neurogenic lineage transient amplifying Type II cells show the expression of glial markers including the transcription factor SRY (sex determining region Y)-box2 (Sox2). At later stages differentiating progenitors express neuronal transcription factors like NeuroD (neurogenic differentiation) (Kronenberg et al. 2003; Seki 2002) and immature neurons express the microtubule-associated protein doublecortin (DCX) (Brown et al. 2003b).



**Fig. 1** Hippocampal neurogenesis in the adult rodent brain follows distinct developmental stages. (Top) Schematic depiction of developmental stages of hippocampal neurogenesis including proliferation, differentiation, maturation, and integration of newborn neurons. (Middle) The morphological development of neurons monitored by GFP expression upon retrovirus-mediated gene transduction in the adult mouse brain. (Proliferation: *left panel*, 3 days postinjection (dpi); differentiation, *middle panel*, 7 dpi, differentiation, mature granule neurons, *right panel*, 28 dpi). Experiments performed by RJ as a fellow in the laboratory of Prof. Dr. Dieter Chichung Lie. (Bottom) Depiction of known and potential CNS receptors/targets modulating the process of adult neurogenesis at the proliferation and differentiation stages *in vivo*

The trajectory of functional maturation includes formation of synaptic connections and the switch from depolarizing to hyperpolarizing action of the neurotransmitter GABA. In particular, while immature adult-born neurons receive

synaptic excitatory GABA inputs (Ge et al. 2006, 2007; Karten et al. 2006), at later stages GABAergic inputs become gradually hyperpolarizing (Ge et al. 2006). Concomitantly, immature neurons form spines and receive glutamatergic excitatory inputs and develop mossy fiber boutons around 4–8 weeks after birth (Faulkner et al. 2008).

Adult hippocampal neurogenesis is not exclusive to rodents, but has repetitively been shown to occur in humans (Knoth et al. 2010; Eriksson et al. 1998). In adult humans around 700 new neurons per day are being integrated per dentate gyrus. This corresponds to an annual turnover rate of 1.75 % of the renewing dentate granule cell population (Spalding et al. 2013). This significant number of new hippocampal granule neurons in humans, together with dynamic regulation under physiological conditions, suggests that adult neurogenesis may be integral to brain functions.

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## **2 Factors Affecting Hippocampal Neurogenesis and Plasticity and Correlation to Cognition**

Over the past 15 years, substantial converging evidence has indicated that neurogenesis in the adult hippocampus is functionally relevant to hippocampal-dependent cognition. Many factors that modulate cognition, including pharmacological agents and intrinsic pathways involved in brain plasticity, as well as physiological stimuli such as running, learning, and enriched environment, also modulate hippocampal neurogenesis. Multiple studies impairing proliferation and adult neurogenesis in the dentate gyrus using various approaches such as chemically and irradiation-induced blockade of proliferation, genetic ablations of progenitor cells, and optogenetic physiological silencing have demonstrated that neurogenesis contributes to hippocampus-dependent learning and memory. In addition, specifically increasing the amount of newborn neurons in the dentate gyrus improves cognitive processes associated with the hippocampus. We will highlight the role of adult neurogenesis in cognition and discuss intrinsic and extrinsic factors regulating the process of neurogenesis.

### **2.1 Cognitive Behaviors Dependent on Hippocampal Function**

Early evidence of the role of the hippocampus in memory and learning comes from studies in humans showing that bilateral resection or damage of hippocampus and hippocampal gyrus leads to memory impairment (Scoville and Milner 1957). Detailed analysis in animal models using functional imaging approaches, lesioning of specific areas of the brain, and circuit tracing reveals that the hippocampus is required for several forms of memory including declarative memory (the ability for conscious remembering) (Squire 1992), episodic memory (remembering of autobiographical events) (Wixted et al. 2014), contextual association memory (Rudy and Sutherland 1995; Lee et al. 2014), and spatial navigation. The hippocampus

combines information about spatial and non-spatial items coming from inputs from the parahippocampal cortex and medial entorhinal cortex and from the perirhinal and lateral entorhinal areas, respectively. In the hippocampus, the dentate gyrus region receives inputs from the entorhinal cortex and DG granule cells project excitatory mossy fibers to the proximal apical dendrites of pyramidal cells in the CA3 area. The dentate gyrus is characterized by structural and functional heterogeneity along the dorso-ventral axis, with the dorsal region being mainly implicated in the regulation of cognition and memory and the ventral region involved in the modulation of mood and stress (Kheirbek et al. 2013; Tannenholz et al. 2014). One major process supported by the dorsal DG is conjunctive encoding which is the processing of multiple unique sensory spatial and non-spatial inputs from the perirhinal cortex and lateral and medial entorhinal cortex to form metric spatial representations (Kesner 2013). Indeed, lesions in the dorsal DG cause impairments in cue-context associations like the ability to associate environmental cues to specific odors (Morris et al. 2013).

Different circuits and regions in the hippocampus are instrumental in the processes of pattern separation and pattern completion, important mechanisms in declarative memory (Yassa and Stark 2011). Pattern separation is the ability to discriminate between similar overlapping representations by differentially encoding small or weak changes from similar inputs such as between two friend's faces (Treves et al. 2008). On the other hand, pattern completion allows accurate reconstruction of incomplete representations based on previously stored representations. The dentate gyrus appears to be critical for the process of pattern separation. This process is facilitated by the distributed pattern of firing activity of the DG cells and the sparse mossy fiber connections onto CA3 pyramidal cells, lowering the probability of two CA3 neurons to receive inputs from the same population of DG neurons (Rolls 1996). On the other hand, local axonal inputs of neurons in the CA3 onto dendrites of cells in the same regions (also called recurrent collaterals) appear to mediate the process of pattern completion. The CA3 area of the hippocampus also receives direct inputs from the entorhinal cortex (perforant path) which are critical for memory retrieval, while inactivation of mossy fiber inputs onto CA3 neurons affects encoding and new learning without altering memory recall (Lassalle et al. 2000; Lee and Kesner 2004; Rolls 2007). In humans, fMRI studies performed during incidental encoding tasks show a correlation between level of activity in the CA3/DG and pattern separation tasks, while activity in CA1, the subiculum, the entorhinal, and parahippocampal cortices correlates with pattern completion (Bakker et al. 2008).

## 2.2 The Role of Hippocampal Neurogenesis in Cognition

How does adult neurogenesis contribute to memory and hippocampal function and why is this so unique to the dentate gyrus? Adult hippocampal neurogenesis has been implicated in several aspects of contextual and spatial memory. For example, in aged outbred rats there is direct correlation between performance in the water

maze test, a hippocampus-dependent spatial learning task, and the amount of neurogenesis in the dentate gyrus. Notably, high performers have a significantly higher number of surviving neurons, based on BrdU (bromodeoxyuridine, a synthetic nucleoside analogue of thymidine incorporated in newly synthesized DNA of replicating cells)-positive cell counting, a readout of proliferation, in the dentate gyrus after learning (Drapeau et al. 2003). Spatial learning tasks such as the Morris water maze modulate hippocampal neurogenesis leading to the question of whether these newborn neurons are integrated in the preexisting memory circuit and reactivated during memory recall.

The evidence that newborn neurons are actively integrated in circuits during specific spatial learning tasks comes from studies analyzing the expression of immediate early genes (like *c-fos* and *arc*), a molecular correlate of neuronal firing activity, in newborn cells generated before or after exposure to spatial learning and birthdated with specific thymidine analogues. Interestingly, newborn neurons generated during a specific development window before exposure to the learning task are preferentially activated upon reexposure to the same spatial learning paradigm if compared to mature dentate granule neurons. These studies suggest that the newborn neurons are preferentially recruited in the generation of specific memory circuits compared to mature dentate granule neurons (Kee et al. 2007; Ramirez-Amaya et al. 2006; Tashiro et al. 2007). The enhanced plasticity of newborn young granule cells could potentially facilitate the integration into new memory circuits and upon maturation the increase in threshold for induction of synaptic plasticity could render the connectivity more stable. Thus, sustained hippocampal adult neurogenesis and continuous maturation of pools of immature neurons allow the DG network to achieve both stable analysis of “old” features and adaptation to new environments, supporting precise and distinct representations of new memories throughout life.

To address the causal relationship between neurogenesis and cognition, studies have focused on the analysis of the effect of neurogenesis ablation or enhancement on behavioral performances. X-ray irradiation-mediated ablation of neurogenesis, as well as genetic ablation in the GFAP-TK genetic mouse model (in which a modified herpes simplex virus gene encoding thymidine kinase under the control of the GFAP promoter causes dividing cells to die upon administration of the drug ganciclovir), leads to impairment in context fear conditioning tasks (Saxe et al. 2006; Drew et al. 2010). In another mouse model, where neurogenesis is ablated selectively inducing the expression of *Bax*, a pro-apoptotic protein, in neural precursors, spatial relational memory is strongly impaired (Dupret et al. 2008). In a mouse model that allowed a transient reduction of the number of adult-born DG cells, it has been shown that reduction of immature neurons confers a deficiency in forming robust, long-term spatial memory and leads to impaired performance in extinction tasks. These results further substantiate that the maturing dentate granule neurons are critical in cognition (Deng et al. 2009). These results were largely confirmed in another study where novel object recognition was impaired by the elimination of 4- to 6-week-old immature neurons (Denny et al. 2012). Recent studies looking at the effect of post-training ablation

(retrograde effects) of newborn neurons and silencing of adult-generated neurons on hippocampal memory further highlight the importance of this neuronal population in formation of memory. Ablation of newborn neurons using a diphtheria toxin-based strategy after learning leads to degradation of existing contextual fear and water maze memories, even when the ablation is induced 1 month after learning (Arruda-Carvalho et al. 2011). Along the same line, using an optogenetic approach, it has been shown that silencing newborn neurons affects the retrieval of memory after completion of training. Interestingly, silencing specifically 4-weeks-old but not younger or older neurons leads to memory impairment. This strongly suggests a functional role of newly integrated immature neurons in the hippocampal circuit (Denny et al. 2012) and supports the hypothesis that immature adult-born neurons contribute to proper cognitive processing.

As cells in the dentate gyrus possess low firing rates and are only activated in a sparse manner, it has been hypothesized that the dentate gyrus may possess a supportive function in pattern separation. Indeed, the ablation of neurogenesis through X-irradiation or Bax overexpression impairs the ability to discriminate between two contexts with overlapping features (Clelland et al. 2009). Importantly, by specifically enhancing the survival of newborn neurons through the deletion of Bax, it has been shown that increase in adult hippocampal neurogenesis does not affect the ability to distinguish between two different contexts but significantly improves the ability to discriminate between overlapping contextual representations (Sahay et al. 2011).

Newborn neurons integrate in preexisting hippocampal circuitry competing with already established synaptic connections. Thus beyond modulating formation of novel memory, adult hippocampal neurogenesis may affect memories already stored in these circuits. Indeed, in many species including humans, during infancy, when the degree of neurogenesis is highest, the retrieval of hippocampus-dependent memories is impaired at later time points (Rubin 2000). Recently, a link between neurogenesis and the ability to forget previously acquired memories has been provided. In this study, using a combination of genetic, pharmacologic, and behavioral strategies, the authors show that increase in neurogenesis after learning is responsible for forgetting and leads to the hypothesis that reconfiguration of hippocampal circuits by newborn neurons may reduce the ability to retrieve previously acquired patterns of activity (Akers et al. 2014).

In conclusion, although there is a certain variability in the effect of modulation of neurogenesis on specific behavioral tasks, a number of studies have consistently shown the causal relationship between neurogenesis and hippocampal-dependent cognitive processes. In the next section, we will review physiological, pathological, and pharmacological mechanisms which can modulate neurogenesis and behavior.



## 2.3 Intrinsic Factors Which Regulate Hippocampal Neurogenesis and Implications in Cognition

Neurogenesis is controlled by interaction of neural progenitor cells and newborn neurons with several components of the dentate gyrus microenvironment, including astrocytes, vasculature, mature granule neurons, and GABAergic interneurons (Song et al. 2002; Palmer et al. 2000; Ma et al. 2009; Ge et al. 2006). Moreover, neurogenesis is tightly regulated by several endogenous signaling molecules including hormones and growth factors. In parallel, the activity of the neuronal network and the release of neurotransmitters from afferent projections onto the dentate gyrus can modulate several aspects of neuronal development. The concerted action of these signaling systems ultimately determines the coordinated functional integration of new neurons in preexisting circuitry (Pathania et al. 2010). Below we will highlight key experimental evidence supporting regulatory roles for some of these factors which are relevant in both physiologically and pharmacologically induced neurogenesis.

### 2.3.1 Neurotransmitters

Neuronal activity strongly modulates various stages of neurogenesis. Lesions of the entorhinal cortex which is one of the major excitatory afferent on granule cells increases DG cells proliferation (Cameron et al. 1995; Nacher et al. 2001). Furthermore, electrical induction of LTP at the perforant path/granule cells synapses promotes proliferation and survival of 1 and 2 weeks old newborn neurons (Bruel-Jungerman et al. 2006; Chun et al. 2006). Glutamatergic neurotransmission and specifically NMDA receptor activity regulates proliferation and correct functional maturation/integration and survival of newborn neurons (Pathania et al. 2010). In tree shrew DG, pharmacological blockade of NMDA receptors leads to increase in the number of BrdU-positive cells (Gould et al. 1997). Along the same line, activation and blockade of NMDA receptors reduce or promote cell proliferation in adult rat DG, respectively. An important question is to what extent this effect is regulated cell-autonomously rather than indirectly via other signals elicited by neuronal activity in the dentate gyrus. Immature neurons have NMDA receptors and express NR1 and NR2B subunits (Nacher and McEwen 2006; Ambrogini et al. 2004). Deletion of the NMDA subunit NR1 in newborn cells reduces the number of properly integrating/surviving newborn neurons. This effect is due to NMDA-dependent regulation of survival during the third week after neuronal birth and it appears to involve a mechanism of competitive survival between the incoming immature neurons and the preexisting neurons. Indeed, global hippocampal reduction in NMDA signaling can rescue the loss of cells. Importantly, maturing neurons (4–6 weeks after neuronal birth) show increased plasticity and reduced threshold for induction of LTP, a process in part mediated by NR2B (Ge et al. 2007). This suggests that glutamatergic signaling plays multiple roles in modulating neurogenesis and controlling the precise integration of newborn neurons into the hippocampal network.

In the SGZ, GABA neurotransmitter, released by specific populations of interneurons, modulates several aspects of neurogenesis, including precursor cells' proliferation, differentiation, and subsequent neuronal maturation. Like in development, there is a switch between depolarization and hyperpolarization effects of GABA while the newborn cells are maturing and this may alter properties of immature neurons including their synaptic plasticity (Ge et al. 2006). The enhanced synaptic plasticity of immature neurons is likely in part due to a lack of strong GABAergic inhibition (Ge et al. 2008; Markwardt and Overstreet-Wadiche 2008; Pallotto and Deprez 2014). Tonic response of nestin-expressing quiescent radial glia cells to GABA released from parvalbumin interneurons regulates their reactivation and entry into the cell cycle. This is mediated by activation of  $\gamma 2$  containing GABA A receptors since conditional deletion of the subunit induces exit from quiescence and promotes symmetric self-renewal of type I cells (Song et al. 2012). The role of tonic GABA transmission on inhibition of cell proliferation is confirmed in another study upon deletion of the  $\alpha 4$  subunit, component of GABA A receptors mediating tonic (extrasynaptic) response (Duveau et al. 2011). Neural progenitors' proliferation is regulated also by GABA B receptors, metabotropic G-protein-coupled receptors located both on pre- and postsynaptic terminals. Both pharmacological blockage and genetic deletion of the B1 subunit of GABA B receptors promote progenitor cells' proliferation (Felice et al. 2012; Giachino et al. 2014). GABA-mediated depolarization, due to high concentration of intracellular  $\text{Cl}^-$  in immature neurons, induces neuronal differentiation and NeuroD expression in transient amplifying neuronal progenitor (type 2) cells (Tozuka et al. 2005). Deletion of both the  $\alpha 4$  and  $\alpha 2$  subunits, a component of GABA A receptors mediating synaptic phasic response, causes reduction of dendritic length and complexity in newborn neurons, which is revealed at different stages of differentiation (Duveau et al. 2011). Altering the GABAergic-dependent depolarization/hyperpolarization switch process by genetically modulating the expression levels of the  $\text{Cl}^-$  importer NKCC1 reveals the key role of this mechanism in the regulation of proper neuronal morphology, differentiation, and synaptic maturation (Jagasia et al. 2009; Ge et al. 2006). The effect of GABA transmission on newborn neurons development is at least in part mediated by activation of downstream signaling events via activity-dependent transcription factors such as CREB (Jagasia et al. 2009).

Loss of cholinergic neurons or blockage of acetylcholine (ACh) receptors in the central nervous system causes learning impairment in experimental and clinical situations in humans (Drachman and Leavitt 1974; Rasmussen and Dudar 1979). Newborn neurons in the dentate gyrus are innervated by forebrain cholinergic fibers (Kaneko et al. 2006) and by septal cholinergic cells as shown using a combination of rabies virus-mediated retrograde tracing and retroviral labeling of new granule cells (Vivar et al. 2012). Neurotoxic and immunotoxic lesion of forebrain cholinergic projections leads to decreased neurogenesis, increased apoptosis and impaired spatial memory (Mohapel et al. 2005; Cooper-Kuhn et al. 2004). Modulation of the cholinergic system using a number of pharmacological approaches further supports the role of the system in regulation of neurogenesis (Veena et al. 2011a).

**Table 1** Examples of pharmacological interventions that improve neurogenesis and cognition

Molecule	Effect on neurogenesis	Effect on cognition	Disease model	References
GABA(A) $\alpha 5$ negative allosteric modulator	Correction of hippocampal synaptic plasticity and adult neurogenesis defects	Correction of spatial learning and memory deficits	Ts65Dn mouse model of Down Syndrome	Martinez-Cue et al. (2013)
Isoxazole-9	Enhancement of proliferation and differentiation of neuroblasts, dendritic arborization of immature neurons	Enhancement of memory in Morris Water Maze		Petrik et al. (2012)
P7C3	Enhancement of survival of newborn neurons	Improvement of performance in Morris water maze task in aged rats	Aging	Pieper et al. (2010)
SB216763 (GSK3 beta inhibitor)	Correction of neuronal differentiation and maturation deficits	Improvement in trace conditioning learning test and spatial learning and memory in DMNP radial arm maze	FMR1 ko mouse model of Fragile X syndrome	Guo et al. (2012)
Lithium (GSK3 beta inhibitor)	Enhancement of progenitor cells proliferation and differentiation	Improvement of performance in Morris Water maze task and inhibitory avoidance task	TgCRND8 mouse model of AD	Fiorentini et al. (2010)
Lithium	Correction of hippocampal synaptic plasticity and adult neurogenesis defects	Correction of deficits in performance in fear conditioning, object location, novel object recognition tests	Ts65Dn mouse model of Down Syndrome	Contestabile et al. (2013)
Compound K	Partial correction of neurogenesis impairment	Improvement in passive avoidance and Y maze tests	Cyclophosphamide-treated mice as model of chemotherapy	Hou et al. (2013)

(continued)

**Table 1** (continued)

Molecule	Effect on neurogenesis	Effect on cognition	Disease model	References
Fluoxetine	Correction of progenitor cells proliferation in the DG	Improvement in contextual fear conditioning tests	Ts65Dn mouse model of Down Syndrome	Bianchi et al. (2010) (NB: early treatment)
Fluoxetine	Correction of reduced progenitors proliferation in the DG	Improvement in hippocampal-dependent spatial working memory	5-fluorouracil-treated rats as model of chemotherapy	ElBeltagy et al. (2010)
Imipramine	Preservation of proliferation and survival of newborn neurons	Improvement in novel object recognition test	Mouse model of traumatic brain injury	Han et al. (2011)
Amitriptyline	Increase in neurogenesis and BDNF signaling	Improvement in short- and long-term memory retention	3xTgAD mouse model of AD	Chadwick et al. (2011)
Metformin	Increase in neurogenesis	Improvement in spatial reversal learning		Wang et al. (2012)

Stimulation of cholinergic receptors with the cholinergic agonist physostigmine and inhibition of acetylcholinesterase using donepezil induces neurogenesis and promotes proliferation and short-term survival (Mohapel et al. 2005; Kaneko et al. 2006; Kotani et al. 2006). On the other hand, scopolamine, a cholinergic muscarinic receptor blocker, decreases the number of BrdU-positive cells in the DG affecting the survival of newborn neurons (Kotani et al. 2006). Early in their development, adult-born neurons express homomeric  $\alpha 7$ -containing nicotinic acetylcholine receptors and cell autonomous genetic ablation leads to impairment in dendritic maturation and synaptic integration ultimately resulting in reduced survival (Campbell et al. 2010). In global knockout models of the  $\beta 2$  receptor subunit there is significant reduction in cell proliferation culminating in a net reduction in the size of the dentate granule cell layer (Harrist et al. 2004). In vitro, cholinergic stimulation affects proliferation and survival of rat olfactory bulb and cortical neural precursor cells (Coronas et al. 2000; Ma et al. 2000). Acetylcholine neurotransmission appears to be deregulated with age and in Alzheimer's disease, conditions with reduction in both neurogenesis and cognitive capacity. Notably, pharmacological modulation of the cholinergic activity in aged or stressed animals promotes NSCs' proliferation and corrects cognitive alterations (Itou et al. 2011; Veena et al. 2011b).

The dopaminergic system has been shown to affect proliferation and differentiation of neural progenitor cells during embryonic development and in both adult neurogenic zones. Lesion and pharmacological studies in the SGZ have yielded

discrepancy in results (Veena et al. 2011a). Focusing on the pharmacological approaches, depletion of dopamine in rodents reduces proliferation of SGZ neuronal precursor cells and this is reversed by treatment with a D2-like receptor agonist (Hoglinger et al. 2004). Similarly, activation of D2 receptors using quinpirole promotes NSCs' proliferation (Yang et al. 2008). However, administration of haloperidol, a D2-like receptor antagonist, has been reported to induce both positive and negative effects on neurogenesis in the SGZ (Wakade et al. 2002; Wang et al. 2004; Keilhoff et al. 2010; Halim et al. 2004). A recent study demonstrates that dopamine increases adult hippocampal NSCs' proliferation acting on D1-like receptors since the effect is phenocopied by a D1-like receptor agonist but not a D2 agonist (Takamura et al. 2014). On the other hand, stimulating the D3 receptor appears to exert an inhibitory effect on neurogenesis since inhibition of the D3 receptor using the antagonist S33138 increases cell proliferation in the hippocampus and the results are replicated in a D3 KO mouse model (Egeland et al. 2012).

Serotonin and noradrenaline, as well as antidepressant drugs that influence their neurotransmission, play a key role in the regulation of hippocampal neurogenesis and hippocampal-dependent behaviors. This class of molecules will be described more in detail in the section on depression and antidepressant treatments. In Table 1 are listed examples of pharmacological manipulations that have been demonstrated to induce changes in neurogenesis and cognition.

### 2.3.2 Wnt/Beta-Catenin Pathway

The Wnt signaling pathway is a highly conserved signaling pathway that has been implicated in nervous system development and has multiple functions in the adult brain including a role in hippocampal adult neurogenesis. Disruption of the physiological Wnt signaling pathway has been associated with several CNS pathologies, including schizophrenia, mood disorders, autism, and Alzheimer's disease. A canonical Wnt ligand inhibits glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ), which modulates the degradation of  $\beta$ -catenin. In the presence of extracellular Wnt ligand, and subsequent receptor activation, stabilized  $\beta$ -catenin enters the nucleus and associates with TCF/LEF transcription factors, resulting in transcription of Wnt-target genes (Varela-Nallar and Inestrosa 2013).

Based on *in vitro* and *in vivo* results, it has been demonstrated that Wnt/ $\beta$ -catenin signaling regulates adult hippocampal NPC proliferation and differentiation (Lie et al. 2005; Kalani et al. 2008). In the hippocampus, lentivirus-mediated expression of Wnt3 or a dominant-negative form of WNT (dnWNT), respectively, increases and almost abolishes adult neurogenesis. Furthermore, expression of dnWNT impairs both long-term retention of spatial memory in the water maze task and performance in a hippocampus-dependent object recognition task (Jessberger et al. 2009). Importantly, the levels of neurogenesis correlate with the performance on specific memory tasks.

Wnt signaling is modulated in diverse physiological conditions characterized by changes in the rate of hippocampal adult neurogenesis. The relationship between aging, neurogenesis, and cognitive impairment will be described in later sections. For example, Wnt signaling shows a reduction during aging when neurogenesis is

decreased and, most importantly, modulation of the pathway can counteract age-related neurogenesis and cognitive declines. Aged astrocytes show a reduced expression of multiple canonical Wnt molecules, which in part results in a reduction of adult hippocampal neurogenesis (Miranda et al. 2012). Moreover, the expression of the Wnt antagonist Dickkopf-1 (Dkk1) increases with age and inducible deletion of Dkk1 enhances neurogenesis. Aged mice with a loss of Dkk1 exhibit enhanced spatial working memory and memory consolidation (Seib et al. 2013). Conversely, activity-dependent induction of neurogenesis using electroconvulsive shock leads to reduction in the expression of secreted frizzled-related protein 3 (sFRP3), a naturally secreted Wnt antagonist, in mature dentate granule neurons (Jang et al. 2013a). Deletion of sFRP3 induces the proliferation of precursor cells and promotes newborn neurons maturation, dendritic growth, and dendritic spine formation in the adult mouse hippocampus.

Modulation of Wnt signaling appears to be of therapeutic relevance also in disease conditions. Indeed, sFRP3 deletion alone is sufficient to induce an antidepressant-like behavioral response on the same magnitude of known antidepressants, whose effect, as we will describe later, is at least in part linked to neurogenesis (Jang et al. 2013b). Moreover, in mouse models of Alzheimer's disease characterized by impairment in neurogenesis, treatment with lithium, a pharmacological activator of Wnt/ $\beta$ -catenin signaling acting via GSK3- $\beta$  inhibition, ameliorates memory loss (Toledo and Inestrosa 2010). In a recent study, in vivo administration of both WASP-1, an activator of Wnt/ $\beta$ -catenin signaling, and FOXY-5, an activator of both Wnt/JNK and Wnt/ $\text{Ca}^{2+}$  signaling, improves hippocampal-dependent learning and memory processes (Compton et al. 2011). Wnt signaling enhancers would be potentially highly relevant cognitive therapies targeting hippocampal neurogenesis.

### 2.3.3 Neurotrophic Factors: The Role of BDNF

Neurotrophic factors are extracellular signaling proteins that play critical roles in both the developing nervous system and in adult brain physiology. BDNF and its role in hippocampal neurogenesis have been studied more extensively than any of the other neurotrophins. Chronic infusion of BDNF in the hippocampus of adult rats promotes cell proliferation and neurogenesis (Scharfman et al. 2005). The induction of neurogenesis by BDNF appears to be region specific since it does not affect the process in the SVZ, the other neurogenic niche in the adult rodent brain (Galvao et al. 2008). BDNF affects also later stages of neuronal maturation. Indeed, deletion of TrkB, the receptor of BDNF, in adult neuronal progenitor cells in the hippocampus leads to impairment in dendritic and synaptic growth in newborn neurons and deficits in neurogenesis-dependent LTP (Bergami et al. 2008).

BDNF plays a key role in hippocampus-dependent functions associated with roles in cognition and mood regulation, which will be further discussed in later sections. For example, in pattern separation inhibition of BDNF by infusion of a BDNF-blocking antibody or by antisense oligonucleotide-mediated knockdown impairs the ability to encode and consolidate "pattern separated" memories. On the other hand, acute infusion of recombinant BDNF enhances the separation of

representations (Bekinschtein et al. 2013). The effect of BDNF on pattern separation performance is mediated by newborn immature neurons since BDNF infusion has no behavioral effect when neurogenesis is reduced by overexpression of dnWNT (Bekinschtein et al. 2014). As we will describe in more detail later, intact BDNF signaling is critical for learning, exercise, and antidepressants' treatment-induced increase in neurogenesis and effect on behavior (Rossi et al. 2006; Li et al. 2008). BDNF-based therapies would be highly relevant to increase neurogenesis activity and hippocampal function associated with cognition.

## **2.4 Physical Exercise and Learning: Effect on Hippocampal Neurogenesis, Synaptic Plasticity, and Cognition**

The CNS is known to undergo cellular, molecular, and functional changes in response to external social, cognitive and physical stimuli. Voluntary physical exercise has been shown to have beneficial effects on memory and cognition in physiological and pathological conditions in rodents and in humans (Voss et al. 2013). Interestingly, the cognitive amelioration is paralleled by increase in hippocampal neurogenesis and synaptic plasticity. In this section, we will review the effects of exercise on cognitive performance focusing on hippocampal-dependent behaviors and we will describe the effects on adult neurogenesis and synaptic plasticity.

### **2.4.1 Exercise and Enriched Environment in Animals: From Cognition to Neurogenesis**

In adult rodents, physical exercise and exposure to enriched environment (EE), a complex combination of cognitive, physical and social stimulation, improve cognitive functions. Running and EE ameliorate performance in tasks of contextual fear conditioning, novel object recognition, and passive avoidance learning and in tasks assessing hippocampus-dependent memory like spatial memory in the Morris water maze and pattern separation (Kempermann et al. 1997; Fordyce and Farrar 1991; Falls et al. 2010; O'Callaghan et al. 2007; Creer et al. 2010). Hippocampal neurogenesis is one of the most remarkable changes in cellular and synaptic brain plasticity correlating with cognitive improvements upon exercise and EE. The first study analyzing the correlation between exercise and neurogenesis demonstrated that mice housed in an enriched environment with access to a running wheel exhibited better performance in Morris water maze tasks and have a 15 % increase in granule cell neurons in the dentate gyrus (Kempermann et al. 1997). BrdU birthdating experiments in mice show that cell proliferation peaks after 3 days of running, and the effect is still sustained at 10 days (Kronenberg et al. 2006; van der Borght et al. 2006). Running affects cell cycle kinetics of various subpopulations of newborn neurons. It induces both proliferation and cell cycle exit of DCX-positive type 3 precursors, shortens cell cycle in NeuroD1-positive progenitors, and even activates proliferation of radial type 1 stem cells (Brandt et al. 2010; Farioli-Vecchioli et al. 2014; Lugert et al. 2010). Exercise and EE appear to affect specific

stages of the neurogenic process. In a study dissecting the role of learning and exercise on neurogenesis, voluntary exercise increases cell proliferation and integration/survival while exposure to an enriched environment, including access to a running wheel, only affects newborn neurons integration/survival in mice (van Praag et al. 1999b). In another study focusing on the effect of different learning paradigms on neurogenesis, the number of adult-generated neurons doubles in the dentate gyrus of rats trained on hippocampus-dependent associative learning tasks like spatial navigation in a Morris water maze and conditioning of the eye blink response using a trace protocol. Learning tasks that do not require the hippocampus fail in eliciting neurogenesis changes. These results suggest that to affect neurogenesis in the hippocampus, animals need to be trained on learning tasks for which the hippocampus is essential (Gould et al. 1999). The increase in newborn neurons upon learning appears to be due to enhanced survival and or integration rather than proliferation (Gould et al. 1999; Kee et al. 2007). Interestingly, a sequential combination of running and EE in mice leads to a 30 % greater increase in neurons than either stimulus alone. This suggests that coupling a stimulus like running which induces precursor cell proliferation to a survival-promoting stimulus like EE can enhance neurogenic pool and then subsequent integration (Fabel et al. 2009). Moreover, the effect of physical exercise and learning on neurogenesis appears to be region specific since generation of new neurons is not observed in the subventricular zone or in the cortex (Brown et al. 2003a; Gould et al. 1999; Ehninger and Kempermann 2003). Studies aimed at understanding whether neurogenesis is necessary for the beneficial effect of exercise and EE on cognition have yielded contradictory results. Reduction of neurogenesis using the antimetabolic agent methylazoxymethanol acetate (MAM) in rats prevents the improvement in long-term recognition memory in a novel object recognition task upon EE (Bruehl-Jungerman et al. 2005). In mice, gamma irradiation-mediated reduction in neurogenesis has a behavior-specific effect: while running-induced improvements in motor performance (rotarod) and contextual fear conditioning are not affected, spatial memory amelioration is ablated in the absence of neurogenesis (Clark et al. 2008). Interestingly, in very old mice (22 months old) with physiological reduction of neurogenesis which is no longer induced by running, the improvement in spatial pattern separation by voluntary exercise seen in young mice is lost (Creer et al. 2010). However, another study in mice shows that the improvement in spatial learning and the decrease in anxiety-like behavior upon EE are not affected by irradiation-mediated reduction of neurogenesis (Meshi et al. 2006). While several methodological and species differences might contribute to the discrepancies, this work suggests that cognitive improvement might be mediated also by neurogenesis-independent mechanisms such as increase in neurotrophic factors and induction of neuronal and synaptic plasticity.

Upon exercise several growth factors relevant for neuronal function and plasticity like NGF (Neeper et al. 1996), IGF-1 (Carro et al. 2000; Trejo et al. 2001), FGF2 (Gomez-Pinilla et al. 1997), and BDNF are upregulated. The levels of BDNF are increased upon both short- and long-term exercise paradigms (Molteni et al. 2002; Berchtold et al. 2005; Ding et al. 2011) and the increase is sustained up to 2 weeks



after exercise has ended in mice (Berchtold et al. 2005). In rats exposed to voluntary running the expression of BDNF in the hippocampus and neocortex positively correlates with the mean distance run per night (Neeper et al. 1996). BDNF is increased in the dentate gyrus also in response to a forced treadmill-running training and this correlates with improved object recognition learning (O'Callaghan et al. 2007). Interestingly, while the performance in this learning task is improved both upon exercise and EE, only exercise can induce an increase in BDNF expression and cell proliferation (Bechara and Kelly 2013). Importantly, genetic ablation of the BDNF receptor TrkB in hippocampal neural progenitor cells ablates neurogenesis in response to exercise (Li et al. 2008). These results indicate that exercise induces BDNF expression, which results in increased neurogenesis in the DG. Interestingly, peripheral neutralization of VEGF abolishes running-induced neurogenesis potentially affecting angiogenesis, a process required in the modulation of the neurogenic niche to sustain greater cell production (discussed below in more detail) (Fabel et al. 2003).

Exercise-induced increase in BDNF often accompanies changes in synaptic plasticity and expression of genes important for neuronal activity and synaptic function (Tong et al. 2001). Voluntary running in rats induces expression of BDNF, NR2B subunit of NMDA receptor, and glutamate receptor 5 and concomitantly alters the induction threshold for synaptic plasticity leading to enhanced short- and long-term potentiation (LTP) in the dentate gyrus (Farmer et al. 2004). In another study, expression analysis in the whole hippocampus after 3 and 7 days of exercise shows an upregulation of NR2A (Molteni et al. 2002), a subunit shown to be necessary for exercise-induced neurogenesis in a genetic mouse model (Kitamura et al. 2003). Similarly, recordings in hippocampal slices from mice exposed to running show an enhancement of LTP specifically in the dentate gyrus (van Praag et al. 1999a). Synaptic transmission properties in the DG and the CA1 area of the hippocampus are modified also in response to learning and EE. For example, electrophysiological recording in freely moving rats shows increase in fEPSPs and in granule cell excitability in the dentate gyrus upon EE exposure (Irvine et al. 2006).

Exercise and learning also affect the morphological maturation of newborn neurons and the structure of already existing neurons in the hippocampus. In newborn DG neurons, running accelerates the formation of mushroom spines and alters spines motility early during differentiation without affecting the total spine density (Zhao et al. 2006). Spatial learning in the Morris water maze increases dendritic arbor complexity in both immature and mature newborn neurons, between 3 weeks and 4 months after birth (Lemaire et al. 2012). Interestingly, spatial and non-spatial environmental cues affect spine morphogenesis in a layer-specific fashion in the DG. Spatial cues induce mushroom spine formation in the middle molecular layer of newborn neurons that receive inputs from the entorhinal cortex (EC) providing spatial information. Conversely, non-spatial components increase mushroom spine formation in the outer molecular layer receiving inputs from the lateral EC (Zhao et al. 2014). Voluntary exercise affects dendritic complexity and spine density not only in the DG but also in afferent populations like pyramidal

neurons in the CA1 and layer III pyramidal neurons of the entorhinal cortex (Redila and Christie 2006; Stranahan et al. 2007).

Another brain structural change that correlates with and indirectly supports the increase in neurogenesis is angiogenesis. The brain vasculature is a key component of the neurogenic niche providing extrinsic signals for progenitor cells that are closely associated with blood vessels. Moreover, angiogenic factors can stimulate neurogenesis. Exercise enhances blood flow and blood vessels growth throughout the brain and in the dentate gyrus (Black et al. 1990; van Praag et al. 2005). The growth is at least in part supported by increased expression of angiogenic factors like IGF-1 and VEGF and correlates with increased neurogenesis (Fabel et al. 2003). Intriguingly, experiments using parabiotic animals have identified blood-derived factors that directly regulate neurogenesis in a positive or negative manner, pointing toward systemic factors influencing neurogenesis in adults (Villeda et al. 2011, 2014; Katsimpardi et al. 2014). Interestingly, MRI studies show that increased cerebral blood volume (CBV) in the dentate gyrus can be used as an *in vivo* correlate of neurogenesis and it is specifically affected by exercise in mice. These findings are confirmed in human where dentate gyrus CBV correlates with cardiorespiratory fitness and cognitive function (Pereira et al. 2007). These data suggest that CBV measurements could represent a correlative biomarker for neurogenesis in humans.

#### **2.4.2 Human Neurogenesis, Cognition and Exercise**

Brain imaging studies support the role of the DG/CA3 subfields of the hippocampus in pattern separation in humans. In a study combining functional MRI and ultrahigh-resolution structural MRI, it has been shown that there is a correspondence between CA3 anatomy and functioning and pattern separation, pattern completion and individual differences in episodic memory recall (Chadwick et al. 2014). In non-demented older adults, changes in the activity measured by fMRI in the CA3/DG region correlate with the performance in pattern separation (Yassa et al. 2011). Moreover, DG/CA3 is also involved in pattern separation of emotional information and in patients affected by depression the severity of depressive symptoms negatively correlates with DG/CA3 activity (Leal et al. 2014). As in animals, hippocampal structural changes appear to correlate with training on tasks dependent on the hippocampus. Indeed, the posterior hippocampus stores spatial representations of the environment and people with high dependence on navigational skills like London taxi drivers show increased posterior hippocampal volume (Maguire et al. 2000). These data support the relevance of hippocampal areas and their dynamic regulation in specific cognitive tasks in humans. Although animal studies demonstrate a key role for neurogenesis in pattern separation, the lack of biomarkers for neurogenesis in humans limits conclusive studies. On the other hand, studies in cancer patients show that systemic treatment with chemotherapy agents often results in cognitive impairment and decline in aspects of memory which require hippocampal function. In animal models it has been shown that neural stem cells proliferation in the DG is reduced by chemotherapy, suggesting

this as one of the potential mechanisms underlying some of the cognitive deficits related to the treatment (Wigmore 2013).

Several studies in human suggest that aerobic exercise has a positive effect on cognitive performance in healthy individuals and can counteract cognitive impairment during aging or in pathological conditions (Voss et al. 2013). In the healthy population, aerobic exercise can improve executive functions like task switching, selective attention, working memory updating, and inhibitory control in children and young adults (Guiney and Machado 2013). Cardiovascular fitness positively associates with intelligence assessed using tests for logical, verbal, and technical skills (Aberg et al. 2009; Moore et al. 2014), with increased cognitive flexibility and improved action monitoring process (Themanson et al. 2008; Hillman et al. 2008), and with improvement in academic achievements (Chaddock-Heyman et al. 2013; Chaddock et al. 2012).

Exercise has also been shown to specifically improve performance in cognitive tasks known to critically depend on hippocampal function. Young individuals, exposed to a long-term aerobic exercise regime and experiencing a change in fitness, show better performance in visual pattern separation task, visuospatial memory, and positive affect (Dery et al. 2013; Stroth et al. 2009; Herting and Nagel 2012), relational memory (e.g., children show higher ability to remember pairs of faces and houses studied under relational encoding conditions) (Monti et al. 2012; Chaddock et al. 2010, 2011). Interestingly, magnetic resonance imaging shows that performance in relational and visuospatial memory tasks positively correlates with larger hippocampal volumes, suggesting that structural modifications play a role in improved function (Chaddock et al. 2010; Herting and Nagel 2012).

Physical activity has beneficial effects on cognition also in older adults and in conditions associated with cognitive impairment. Older humans exposed to physical exercise improve executive control processes like planning, scheduling, and working memory (Kramer et al. 1999). Similarly to that observed in younger adults, aerobic fitness correlates with increased hippocampal volume and better spatial memory in older individuals (Erickson et al. 2009). Moreover, a longitudinal study showed that in adults over the age of 65 years physical activity correlates with diminished incidence of Alzheimer's disease. In conditions of memory problems or cognitive impairment, exercise still improves cognitive function and positive behavior (Heyn et al. 2004).

Overall these studies support a positive effect of exercise on cognition and on hippocampus-dependent processes like spatial and relational memory and pattern separation. Importantly, cognitive improvements correlate with structural changes in the hippocampus both in animals and in humans. However, a direct link to neurogenesis in humans is lacking, as currently there is no possibility to measure neurogenesis in living humans.

## **2.5 Depression, Stress, and Antidepressants: Effect on Neurogenesis and Behavior**

### **2.5.1 Cognitive Impairment in Depression**

Depression is a widespread disorder and it presents with symptoms which include, among others, low mood, feelings of despair, reduced attention capacity, and suicidal ideation. Patients affected by major depressive disorder (MDD) show high prevalence of cognitive dysfunction, including hippocampal-dependent cognitive processes. Among the most common deficits are memory disturbances, difficulty in making decisions, and reduced cognitive flexibility (Fava et al. 2006; Wagner et al. 2012; Jaeger et al. 2006; McCall and Dunn 2003). Morphometric analysis in patients diagnosed with first episode MDD shows structural alterations in hippocampus, amygdala, and corticolimbic regions (Frodl et al. 2002; Zhu et al. 2011). MDD patients show impaired performance in tests assessing hippocampal-dependent declarative memory and functional imaging analysis shows abnormal activation of hippocampus during verbal memory encoding task (Bremner et al. 2004). As we will describe in detail later, alteration of the hypothalamic–pituitary–adrenal (HPA) axis and in glucocorticoids (GCs) levels are hallmarks of depression pathophysiology. Although not confirmed in all studies, cortisol levels are found to correlate with cognitive deficits in MDD patients and acute administration of GCs in healthy individuals can compromise long-term memory retrieval (Schlosser et al. 2010; Wolf et al. 2009).

Taken together, there is increasing evidence supporting a role for hippocampal dysfunction in cognitive deficits in MDD. Recent anatomical and functional evidence indicates a dissociation of the dorsal and ventral regions of the hippocampus with the dorsal region being responsible for memory and cognition and the ventral part playing a key role in regulation of mood. How alterations in cognitive functions contribute to MDD pathogenesis and to the recovery process is still unclear. In this sections, we will review the effects of stress and antidepressant treatment on neurogenesis and will discuss the role of neurogenesis in the onset and recovery of behavioral phenotypes.

### **2.5.2 Stress and Neurogenesis**

Stressors are considered as experiences and events which challenge the ability of the individual to adapt. Responses which promote adaptation to stressors include the release of hormones and other cellular factors. However, when the response is deregulated it can induce the activation of pathophysiological processes leading to the onset of neuropsychiatric disorders (McEwen 1998).

Stress has been demonstrated to have deleterious effects on multiple stages of hippocampal neurogenesis, newborn neuron maturation, hippocampal neuron plasticity, and dendritic and synaptic density. Exposure of tree shrews to acute conflict to establish a dominant/subordinate relationship leads to reduction of neurogenesis in the dentate gyrus in the subordinate animal (Gould et al. 1997). Negative regulation of neurogenesis is observed also upon chronic stress paradigms in several animal models. For example, cell proliferation in the dentate gyrus shows

a significant reduction in mice subjected to repeated intermittent social defeats (Yap et al. 2006) and in young adult marmosets after forced prolonged social isolation (Cinini et al. 2014). Besides affecting cell proliferation, chronic stress exposure impairs newborn neurons' survival (Tanti et al. 2013; Dagyte et al. 2011) and induces structural abnormalities like dendritic atrophy in CA3 pyramidal neurons (Watanabe et al. 1992; Sousa et al. 2000). At the behavioral level, animal models subjected to chronic stress develop depression-related behaviors. While the effect of stress on neurogenesis has been widely confirmed in several animal models, the role of neurogenesis in the onset of depressive-like behaviors is still a matter of debate. Ablation of neurogenesis in mice via X-ray irradiation of the hippocampus or via pharmacological intervention does not induce behavioral phenotypes relevant to anxiety or depression (Santarelli et al. 2003; David et al. 2009; Bessa et al. 2009). Genetic ablation of neurogenesis via overexpression of the pro-apoptotic protein Bax leads to increase in anxiety-related behaviors while it does not affect depressive behaviors (Revest et al. 2009). Similarly, cyclin D2 knockout mice which lack neurogenesis do not show impaired performance in the forced swimming test (Jedynak et al. 2014). Conversely, in a transgenic model where increase in survival of newborn neurons is achieved by selective deletion of Bax, there are no differences in anxiety and depressive behaviors (Sahay et al. 2011). In contrast to these findings, ablation of radial cell precursors in a GFAP-TK mouse model (expressing under the control of GFAP promoter herpes simplex virus thymidine kinase which renders mitotic cells sensitive to the antiviral drug valganciclovir) leads to depressive behavior in control conditions and increased anxiety in response to stress (Snyder et al. 2011).

### 2.5.3 Mechanisms Underlying the Effect of Stress on Neurogenesis and Establishment of Depressive Behavior

Several mechanisms have been proposed to mediate the effect of stress on adult neurogenesis and establishment of depressive behavior including alteration in the hypothalamic–pituitary–adrenal (HPA) axis (for a comprehensive review, see Anacker 2014; Bambico and Belzung 2013). Here we will review the evidence supporting a causal link between HPA axis dysfunction and alteration in neurogenesis, synaptic plasticity, and neurotrophic factor signaling in depression.

The hypothalamic–pituitary–adrenal (HPA) axis, part of the neuroendocrine system, plays a crucial role in the response to stress and it is deregulated in depression and chronic stress conditions (Anacker 2014). Upon stress, the hypothalamus releases corticotropin-releasing factor (CRF) which stimulates the pituitary to release adrenocorticotropin (ACTH) which ultimately leads to the synthesis and release of glucocorticoids (GCs) from the adrenal cortex. GCs then bind to their intracellular receptors, namely mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs). Upon chronic stress, the HPA axis is hyperactive and leads to chronically high levels of glucocorticoids (Anacker and Pariante 2012). Recent anatomical studies have shown that projections from the ventral hippocampus mediate an inhibitory effect on the hypothalamus, whereas the dorsal hippocampus projects to cortical areas where cognitive processes are mediated. Studies in preclinical models support a

strong causative link between stress, glucocorticoids, and neurogenesis. Exposure of adult rats to predator odor induces rise in adrenal hormones levels and decrease in neurogenesis which is prevented blocking the increase of corticosterone by adrenalectomy (Tanapat et al. 2001). Interestingly, chronic corticosterone treatment induces depressive behavior in rodents (Gourley and Taylor 2009) and affects cell proliferation reducing the number of BrdU-positive cells in the dentate gyrus in adult mice (David et al. 2009). Besides reducing neurogenesis, it has been proposed that stress and corticosterone treatment promote a cell fate switch of nestin-positive neural stem cells in the DG toward increased oligodendrocytes' differentiation (Chetty et al. 2014). Interestingly, corticosteroid levels and expression of the receptors are also altered during aging, a physiological situation with reduced neurogenesis (Gupta and Morley 2014).

Patients affected by major depressive disorder (MDD) show increased cortisol levels, impaired feedback response to GR activators, and correlation between genetic variation in components of the HPA pathway and clinical manifestations (Young et al. 1991; Belvederi Murri et al. 2014; Schatzberg et al. 2014). Volumetric analysis reveals alterations of several brain regions involved in the control of the HPA axis in MDD patients, like significantly increased volume of adrenal gland and reduced volume of hippocampus (MacMaster et al. 2014; Sheline et al. 1996). At the cellular level, expression of synaptic proteins regulating synapse function and structure as well as glutamate receptor subunits is altered in hippocampi and prefrontal cortex from MDD patients' brains (Duric et al. 2013; Fatemi et al. 2001; Kang et al. 2012). Interestingly, this correlates with alterations in the expression of neurotrophic factors important for the function and plasticity of synapses. Expression levels of BDNF, NGF, and their relative receptors are decreased in hippocampi and PFC from suicide victims (Banerjee et al. 2013; Pandey et al. 2008) and MDD patients (Dunham et al. 2009). Moreover, serum levels of micro-RNAs associated with the regulation of expression of BDNF are altered in depressed patients (Li et al. 2013). Although the mechanisms which link stress and alterations of neurotrophic factors' levels are not completely understood, several studies show that antidepressant treatment corrects neurotrophins levels and that normal BDNF signaling is necessary for antidepressant action (Castren et al. 2007; Adachi et al. 2008). This suggests that these factors play an important role in restoring the physiological function of networks involved in mood disorders (Duman and Duman 2015).

#### **2.5.4 Antidepressants, Neurogenesis, and Synaptic Plasticity**

For long time, one of the dominant hypothesis to explain the mechanisms underlying MDD has been the monoamine hypothesis, mainly supported by the observation that antidepressants (ADs) exerting a pharmacological action on the central monoamine systems (monoamine oxidase A inhibitors/MAOI, tricyclic compounds/TCA, serotonin and norepinephrine reuptake inhibitors) were effective in relieving depressive symptoms (Delgado 2000). According to this hypothesis, reduced activity of monoamine neurotransmission is at the core of the pathophysiology of depression and correction of this dysfunction alleviates disease symptoms (Asberg

1976). Through different mechanisms, several ADs classes in clinical use enhance serotonergic (5-HT) and noradrenergic neurotransmission.

Many preclinical and some human postmortem studies demonstrate that antidepressant treatment induces an increase in neurogenesis. Malberg and colleagues showed that chronic but not acute fluoxetine treatment increases the number of dividing cells in the dentate gyrus in rats as measured by BrdU incorporation, while the survival of newborn neurons does not appear to be altered by the treatment (Malberg et al. 2000). In humans, analysis of postmortem brains from MDD patients shows that SSRI and TCA chronic treatment increases the number of neural progenitors in the anterior and mid-dentate gyrus (Boldrini et al. 2009, 2012). However, another study could not replicate these findings (Lucassen et al. 2010). The precise role of specific serotonergic receptors in SSRI-induced neurogenesis is still under investigation. Genetic ablation of 5-HT<sub>1A</sub> receptor in mouse prevents fluoxetine induction of neurogenesis while a partial reduction is observed with 5-HT<sub>4</sub> receptor-specific antagonist (Santarelli et al. 2003; Mendez-David et al. 2014). Moreover, pharmacological studies show that 5-HT<sub>1A</sub> receptors are involved in regulation of proliferation of neuronal precursors, while 5-HT<sub>2</sub> receptors influence proliferation and promote neuronal maturation (Klempin et al. 2010). Induction of neurogenesis has been reported also upon treatment with antidepressants which do not act directly through the serotonin system suggesting some potential convergence in mechanisms of action. For example, the endocannabinoid receptor ligand cannabidiol (CBD) exerts anxiolytic and antidepressant effects and induces hippocampal progenitor proliferation and neurogenesis in mice (Campos et al. 2013). Increase in BrdU-positive cells is observed in the dentate gyrus of mice treated with an antidepressant antagonist of group II metabotropic glutamate receptor (Yoshimizu and Chaki 2004). Moreover, non-pharmacological interventions which elicit an antidepressant response like electroconvulsive shock strongly promote hippocampal neurogenesis (Malberg et al. 2000). Altogether these data support a correlation between ADs and neurogenesis, but is this convergent cellular response necessary for these drugs to have an effect on behavioral symptoms? Ablation of neurogenesis through X-irradiation of hippocampus prevented certain behavioral effects of fluoxetine (SSRI) and imipramine (TCA) in mice (Santarelli et al. 2003). The causal role of neurogenesis in certain specific behavioral effects of antidepressants has been confirmed in several studies (Surget et al. 2008, 2011). Fluoxetine treatment corrects the behavioral and neurogenesis defects in mice exposed to chronic corticosterone treatment and ablation of neurogenesis impairs amelioration in novelty suppressed feeding test, while open field and forced swim test performances are neurogenesis independent (David et al. 2009). Recently, the antidepressant action of cannabidiol has been shown to require neurogenesis since its effects are not observed in GFAP-TK mouse models (Campos et al. 2013). On the other hand, the behavioral effects of a vasopressin V<sub>1b</sub> antagonist and a CRF1 antagonist (corticotropin-releasing factor 1) which reverse stress-induced suppression of neurogenesis in models of depression appear to be neurogenesis independent (Alonso et al. 2004; Surget et al. 2008).

Chronic antidepressant treatment leads to an increase in the expression levels of neurotrophic factors in the hippocampus and cortical regions, including VEGF, FGF2, and BDNF and its receptor *trkB* which in turn can positively regulate the hippocampal cellular response (Warner-Schmidt and Duman 2007; Mallei et al. 2002). Taking advantage of genetic mouse models designed to have reduced BDNF signaling (heterozygous BDNF knockout or inducible ablation of *trkB* receptor in NPC), it has been demonstrated that a BDNF response is necessary for modulation of newborn hippocampal neurons upon chronic imipramine treatment (Li et al. 2008; Sairanen et al. 2005). In addition, behavioral response to antidepressant treatment is impaired in mice with altered BDNF signaling and with conditional ablation of BDNF in forebrain regions (Saarelainen et al. 2003; Monteggia et al. 2004). These data suggest that increasing BDNF activity is a key mechanism mediating antidepressant action.

Interestingly, the BDNF signaling pathway is upregulated in the hippocampus and PFC shortly after treatment with fast-acting antidepressants (Zhou et al. 2013b; Yang et al. 2013; Autry et al. 2011) and it is associated with functional synaptic changes (Tizabi et al. 2012). Ketamine, an antagonist of *N*-methyl-D-aspartate (NMDA) receptors, exerts antidepressant action within few hours after administration with effects lasting up to 2 weeks in depressed patients (Zarate et al. 2006; Price et al. 2009). Administration of NMDA antagonists leads to rapid translation of BDNF in mouse hippocampus and the antidepressant effect is ablated in BDNF conditional knockout mice (Autry et al. 2011). Interestingly, miR-206 regulates the expression of BDNF in response to ketamine (Yang et al. 2014). In light of the role of BDNF in modulation of synaptic plasticity and the increase in BDNF in the hippocampus upon ketamine treatment, it is tempting to speculate that changes in hippocampal synaptic plasticity may contribute, together with other brain regions, to rapid-onset antidepressant effect. However, this hypothesis still needs to be tested.

### 2.5.5 Antidepressants and Cognitive Impairment

As mentioned above, MDD is associated with alterations in hippocampal-dependent cognitive processes. Since antidepressant treatments have been shown to improve BDNF signaling and neurogenesis, key processes in hippocampus-dependent cognitive functions, antidepressants could potentially ameliorate cognitive symptoms in MDD patients. However, clinical studies have not yielded conclusive results and discrepancies are often attributed to limited study design. Longitudinal studies report persistent cognitive dysfunction in patients after remission from depressive symptomatology (Trivedi and Greer 2014; Hasselbalch et al. 2011; Kuny and Stassen 1995; Weiland-Fiedler et al. 2004; Neu et al. 2005). In one study, cognitive functions have been monitored in patients treated with escitalopram (SSRI) or duloxetine (SNRI); an improvement in working memory, processing speed, and visual episodic memory was best observed with duloxetine (Herrera-Guzman et al. 2009, 2010). To further address the effects of antidepressants on cognitive improvement more studies are needed and understanding this relationship would help design new and more efficacious therapeutic



interventions (Goeldner et al. 2013). Along the same line, more research is needed to unravel the role of hippocampal network and neurogenesis in the onset and recovery of cognitive alterations in MDD.

## **2.6 Cognition and Adult Hippocampal Neurogenic Axis in Physiological and Pathological Aging**

Cognitive functions decline with age and are impaired in pathological conditions associated with advanced age like Alzheimer's disease. Impairment of hippocampus-dependent cognitive processes often correlates with structural and functional changes in this brain region and with alterations in neurogenesis. This sections highlights the relevance of neurogenesis in physiological aging and associated cognitive decline in human and animals. Furthermore, the potential pathophysiological role of neurogenesis in cognitive deficits in Alzheimer's disease is highlighted.

### **2.6.1 Aging and Cognitive Decline in Human: Correlation with Hippocampal Changes**

In human, aging affects a broad range of cognitive functions like executive functions (task switching, updating, inhibition) associated with the prefrontal cortex, episodic memory (memory for events which include specific temporal and spatial context) associated with prefrontal cortex and medial temporal lobes, information processing speed, specific aspects of language, and visuospatial functions (for a review, see Alexander et al. 2012). Several studies report specific alterations in hippocampus-dependent processes. Older individuals show impairment in spatial navigation tasks designed to specifically assess hippocampus-dependent ability to develop a cognitive map (a mental representation of the landmarks and paths in the environment) and to use it to reach any target location by any route available (Iaria et al. 2009). These cognitive deficits often correlate with functional and structural alterations in the hippocampus. For example, older individuals tested in a virtual spatial navigation task show differential activation of several brain areas, as measured by voxel-based analysis, if compared to younger controls. Among those differences, old participants show a reduced activation of hippocampus and parahippocampal gyrus (Moffat et al. 2006). Similarly, impairment in hippocampus-dependent spatial and non-spatial functions and recognition memory has been shown to correlate with decreased hippocampal volume and neurochemical properties in older individuals (Driscoll et al. 2003). Along the same line, a specific correlation between hippocampal volume and wayfinding skills (generation and use of a cognitive map) has been described in older individuals (Head and Isom 2010). Moreover, older adults show performance decline compared to younger control individuals in pattern separation task and a bias toward pattern completion. High-resolution (1.5 mm isotropic) blood-oxygenation level-dependent fMRI analysis reveals an altered activation in the CA3/dentate gyrus regions during trials (Yassa et al. 2011). However, a

meta-analysis of the correlation between hippocampal size and episodic memory in older adults reveals extremely weak correlation (Van Petten 2004). Moreover, while some studies show a progressive change in the volume of several brain regions including shrinkage of the hippocampus (Raz et al. 2010), others show an age-dependent decline in temporal cortex but not in hippocampal volume (Sullivan et al. 2005).

Moving from the neuroanatomical to the cellular level, early analysis with stereological techniques showed no neuronal loss in several areas of the hippocampus during aging (West et al. 1994). On the other hand, neurogenesis appears to decline with age. The expression of neurogenesis markers and the number of DCX-positive cells are decreased in the dentate gyrus in post-mortem human brains from older donors (Knoth et al. 2010). Moreover, birthdating experiments based on measurements of genomic DNA incorporation of  $^{14}\text{C}$ , liberated in the atmosphere during atom bomb testing, show that adult hippocampal neurogenesis in the human brain undergoes a modest decline during aging (Spalding et al. 2013). Whether neurogenesis decline contributes to cognitive deficits in elderly humans remains an open question, although studies in rodents suggest that it might have a significant impact.

### **2.6.2 Age-Related Cognitive and Neurogenesis Decline in Animals**

Decline of cognitive functions has been described in aged rodents and non-human primates. Deficits include impaired performance in spatial learning and memory (Barnes 1979; Gage et al. 1984; Rapp et al. 1997; Lazarov and Marr 2013). Structural MRI analysis shows that hippocampal volume does not change with age (Shamy et al. 2006). However, histologic evaluation shows an imbalance in the volume of different areas of the hippocampus in aged rats with a relative reduction of the volume of the middle portion of the molecular layer (Rapp et al. 1999). Interestingly, early studies demonstrated that in rodents neurogenesis in the subgranular zone declines with age (Seki and Arai 1995; Kuhn et al. 1996; Ben Abdallah et al. 2010) with the major decline taking place during adulthood, before aging (Rao et al. 2005; Demars et al. 2013). Whether the decline in neurogenesis correlates with cognitive impairment is a matter of debate. Studies show that aged rats performing better in Morris water maze and hippocampus-dependent tasks have higher number of proliferating cells and newborn neurons (Driscoll et al. 2006; Drapeau et al. 2003). On the other hand, others show no correlation or negative correlation between the number of proliferating cells and performance in Morris Water Maze in aged rats (Merrill et al. 2003; Bizon et al. 2004). Interestingly, in middle-aged (12 months old) rats, despite the massive reduction of progenitor cell proliferation and newborn cells survival, no deficits in trace fear conditioning are observed (Cuppini et al. 2006).

Several hypotheses have been put forward to explain the mechanisms accounting for neurogenesis decrease in aging and they include both cell-autonomous and non-cell-autonomous processes. Aging is accompanied by changes in the hippocampal stem cell niche vasculature (Hattiangady and Shetty 2008) and reduced expression levels of growth factors important for neurogenesis like VEGF, FGF2, BDNF, and

WNT signaling activity (Shetty et al. 2005; Hattiangady et al. 2005; Bernal and Peterson 2011). Glucocorticoid signaling is altered in aged animals and decreasing corticosterone levels restores the rate of proliferation of neuronal progenitors (Cameron and McKay 1999; Nichols et al. 2001). A heterochronic parabiosis experiment, in which the circulatory system of two animals is connected, shows that blood-borne factors from old mice can induce impairment in synaptic plasticity and cognitive deficits in young animals. Elevated levels of chemokines, including CCL11, are observed in aged animals and increasing peripheral levels of CCL11 in young mice decreases neurogenesis and induces cognitive decline (Villeda et al. 2011). One of the most robust changes observed during aging is a dramatic reduction in progenitor cells' proliferation (Olariu et al. 2007; Walter et al. 2011; McDonald and Wojtowicz 2005; Bondolfi et al. 2004), with the most prominent effect in the ventral hippocampus (Jinno 2011). A meta-analysis comparing the reduction in progenitors' proliferation between different species of rodents, fox, and non-human primates shows that the decline is chronologically equal between species and independent of life span (Amrein et al. 2011). Reduction in neurogenesis in the aged brain has been associated with depletion of the neural stem cells pool as a consequence of their division (Encinas et al. 2011) or to a switch toward a quiescent state (Hattiangady and Shetty 2008; Lugert et al. 2010). Importantly, pro-neurogenic stimuli such as increasing neuronal activity by inducing seizures lead NSCs to reenter the cell cycle and restore proliferation to a level comparable to the one observed in young animals (Lugert et al. 2010). Similarly, exercise and exposure to enriched environment rescue neurogenesis deficits and improve cognitive functions like spatial memory and place recognition memory (van Praag et al. 2005; Kronenberg et al. 2006; Siette et al. 2013). Recently, the chronic administration in aged rats of a blood-brain barrier-permeable peptide derived from the ciliary neurotrophic factor (CNTF), which is known to have neuroprotective properties, restores neurogenesis, synaptic plasticity, and memory (Bolognin et al. 2014). These works suggest that induction of neurogenesis has beneficial effects on cognition during aging. Moreover, targeting the reactivation of neural stem cells in the aged brain could be a promising therapeutic approach to restore cognitive functions. Interestingly, young circulating factors like GDF11, a member of the BMP/TGF $\beta$  family, can restore neurogenesis and proper vasculature also in the SVZ, the other neurogenic niche in the adult brain, and improve olfactory discrimination in aged mice (Katsimpardi et al. 2014).

### **2.6.3 Pathological Aging: Alzheimer's Disease, Cognitive Impairment, and Neurogenesis**

Alzheimer's disease (AD) is an age-related neurodegenerative disease characterized by progressive memory loss and cognitive decline (Caselli et al. 2006). AD represents the most common cause of dementia in the elderly. Pathological hallmarks of the disease are extracellular deposition of amyloid-beta (A $\beta$ ) plaques, excessive phosphorylation of the cytoskeletal protein tau, formation of intraneuronal fibrillary tangles, and neuronal cell loss in the cerebral cortex and hippocampus (Selkoe 2001; Braak and Braak 1991, 1995). The major

environmental risk factor for the onset of the disease is aging, while the greatest genetic factor is apolipoprotein E (ApoE) genotype (Ashford 2004). ApoE exists in three isoforms, with isoform E3 being the wt form and the most common in the population, isoform E2 considered to be protective toward AD, and E4 increasing the risk for the disease and anticipating the age of onset. Hereditary autosomal dominant forms of the disease are caused by mutations in genes encoding for amyloid precursor protein (APP) and presenilin-1 and -2, components of the aspartyl protease  $\gamma$ -secretase complex. Cleavage of APP can follow two pathways: in the non-amyloidogenic pathway cleavage by the protease complex  $\alpha$ -secretase releases the soluble fragment of APP (sAPP $\alpha$ ) and  $\gamma$ -secretase cuts in the intramembrane domain; in the amyloidogenic pathway cleavage by the aspartyl protease  $\beta$ -site APP cleaving enzyme I (BACE1) and by  $\gamma$ -secretase leads to the formation of A $\beta$  (De Strooper and Woodgett 2003; Selkoe and Wolfe 2007).

The hippocampus and the afferent entorhinal cortex show early neuronal loss that correlates with memory decline (Van Hoesen et al. 1991; Gomez-Isla et al. 1996; West et al. 1994, 2004). Patients affected by amnesic mild cognitive impairment (aMCI) and mild AD show reduced performance in hippocampus-dependent tasks like pattern separation (Ally et al. 2013). Importantly, impairment in performance correlates with CSF levels of A $\beta$ 42 and patients carrying the ApoE4 genotype perform worse than others in difficult pattern separation tasks (Wesnes et al. 2014). As discussed previously, performance in pattern separation appears to require hippocampal neurogenesis in the dentate gyrus and growing evidence supports alterations in the neurogenic process in AD. Several proteins associated with AD and mutated in familial forms of the disease are directly involved in the regulation of neural stem cell proliferation and differentiation. Notch1, a master regulator of neural stem cell physiology, is a substrate of PS1/ $\gamma$ -secretase and it is cleaved in response to ligand binding (Alexson et al. 2006; LaVoie and Selkoe 2003; De Strooper et al. 1999). Deletion of *PSEN1*, the gene encoding for PS1 in mice, leads to aberrant neurogenesis during development (Shen et al. 1997). In adult animals, lentiviral-mediated knockdown of PS1 in the dentate gyrus leads to enhanced differentiation of neural stem cells (Gadadhar et al. 2011). Moreover, Notch1 and EGF receptor ligands are substrates of ADAM10, a component of the  $\alpha$ -secretase complex (Hartmann et al. 2002; LaVoie and Selkoe 2003). Neural stem cells' proliferation is regulated also by cleavage products of APP, and the intraventricular injection of sAPP $\alpha$  rescues age-dependent decline in neural progenitors' proliferation (Caille et al. 2004; Demars et al. 2013; Lazarov and Demars 2012).

Studies in several mouse models of AD suggest a strong correlation between alterations in neurogenesis, including neural stem cells' proliferation, newborn neurons' survival and maturation, and disease progression. For example, in the transgenic mouse model Tg2576 which overexpresses the human APP isoform with the Swedish double mutation and develops cognitive defects and amyloidosis, aberrant maturation of newborn neurons is observed already in young age (3 months) and this might lead to altered functional integration of new neurons in the hippocampal circuits (Krezymon et al. 2013). Recently, spatial learning and memory impairments have been described in a knock-in mouse model bearing the

human pathological domain of ApoE4 gene in young age. Neurogenesis appears to be increased in young animals and decreased with age, while apoptotic markers indicate enhanced cell death. Interestingly, these early cognitive and cellular changes take place in the absence of classical AD pathological hallmarks (Adeosun et al. 2014). In another study, deletion of ApoE in mice results in reduced neurogenesis and knock-in of the human ApoE4 leads to impaired maturation of newborn neurons through a mechanism dependent on GABAergic signaling (Li et al. 2009). Comprehensive reviews of neurogenesis phenotypes in AD models can be found elsewhere (Lazarov and Marr 2010; Verret et al. 2007; Mu and Gage 2011).

Analysis of postmortem brain samples from senile AD patients reveals increased expression of newborn neurons markers including DCX in the subgranular zone, granular layer, and CA1 area. These findings suggest that activation of neurogenesis might represent a mechanism of compensation and replacement of degenerated neurons (Jin et al. 2004). In another study, AD brain samples show altered expression of early progenitor markers in the hippocampus, suggestive of enhanced proliferation, while the number of newborn neurons does not appear to be affected (Perry et al. 2012). Plasma and CSF concentrations of stem cell factor, a growth factor exerting neuroprotective effects and supporting neurogenesis, are decreased in AD patients and the level inversely correlates with the degree of dementia (Laske et al. 2008). On the other hand, in pre-senile AD patients no evidence of altered neurogenesis has been detected, while a proliferative change has been observed in glia and vasculature cells (Boekhoorn et al. 2006).

As described above, the hippocampus and the neurogenic process are strongly altered in AD and this might account for some aspects of cognitive decline in patients. However, growing evidence suggests that molecular and structural prerequisites for activity-dependent hippocampal plasticity are preserved in models of AD. Exposure to enriched environment leads to amyloid plaque load reduction and increased expression of genes involved in protective processes and neurogenesis in a transgenic AD mouse model (Lazarov et al. 2005). Similarly, exposure to EE of mice bearing the Swedish mutation in APP reverses spatial learning and memory deficits and this correlates with restoration of some aspects of the neurogenic process. As opposed to the previous study, amyloid load is not affected by EE in this model (Valero et al. 2011). A study dissecting the role of physical activity and cognitive stimuli on neurogenesis in AD shows that while exposure to EE improves neurogenesis and water maze performance in the APP23 mouse model, exercise alone does not show beneficial effect (Wolf et al. 2006). Besides memory and learning impairment, AD is associated with behavioral symptoms that include anxiety and depression. As described previously, the ventral hippocampus is involved in regulation of the response to stress and depressive behavior and neurogenesis might play a role in this process. In a 3xTgAD mouse model bearing mutations in APP, PS1, and Tau genes, restoration of neurogenesis through chronic overexpression of Wnt3a in the ventral region of the dentate gyrus leads to correction of impairments in danger assessment. The effect is neurogenesis

dependent since ablation of neurogenesis via X-irradiation prevents the recovery (Shruster and Offen 2014).

Altogether these works suggest that neurogenesis is pathologically impaired in AD and restoration of the neurogenic process might be a promising therapeutic approach to reverse behavioral and cognitive symptoms in AD patients. Below is highlighted the potential of targeting neurogenesis in disease and drug-discovery approaches for the identification of neurogenic compounds are discussed.

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### **3 Novel Concepts for Targeting Neurogenesis in Cognition and Disease**

As described above, compelling preclinical evidence suggests that hippocampal neurogenesis is modulated by a broad range of physiological and pharmacological stimuli, and most excitingly, *de novo* neurogenesis positively correlates with improved cognitive and emotional states. Three lines of research are emerging that suggest that targeting hippocampal neurogenesis will have translational value in human cognition and warrant future work: (1) recent rodent models demonstrate a cell-autonomous role of neurogenesis in cognition in both physiology and disease; (2) drug screening efforts have led to the identification of novel CNS active compounds with both pro-neurogenic and pro-cognitive effects; and (3) the study of human neurogenesis will potentially lead to the identification of biomarkers to monitor the process in mental illnesses for both diagnostic and therapeutic interventions. Below we highlight discoveries, opportunities, and challenges in these research domains. Research on the role of hippocampal neurogenesis in human physiology and disease will ultimately increase the translational value of this remarkable process of plasticity in the adult human brain.

#### **3.1 Neurogenesis as a Target to Improve Cognition in Physiology and Disease**

Recent studies strongly suggest that the discovery of cell-autonomous signaling pathways that enhance adult neurogenesis may lead to therapeutic strategies for improving memory loss due to aging or injury. Here we highlight some of these pathways relevant for the regulation of neurogenesis and implicated in mental disability and we describe the effect of their modulation on cognitive functions. As previously mentioned, the hippocampus plays a key role in declarative memory functioning as a pattern separator. Genetic modulation of the apoptotic pathway in neural stem cells in the DG through ablation of the pro-apoptotic protein Bax leads to increased neurogenesis and improved performance in pattern separation tasks (Sahay et al. 2011). Future studies using this model in disease-relevant backgrounds (e.g., AD models) could potentially elucidate whether the enhancement of neurogenesis changes significantly disease states.

The ERK pathway is important for the modulation of neurogenesis and cognition. ERK5 is a member of the MAP kinase family and it plays a role in prenatal neuronal development and cell fate specification (Cavanaugh et al. 2001; Finegan et al. 2009; Cundiff et al. 2009). ERK5 is expressed in the adult brain in neurogenic regions and inducible conditional ablation of ERK5 in neural progenitors in the adult brain leads to attenuation of hippocampal neurogenesis (Pan et al. 2012a, b). This correlates with alterations in hippocampus-dependent memory tasks like contextual fear conditioning, with defects in learning flexibility and deficits in pattern separation. Conversely, in a genetic mouse model the activation of ERK5 in neuronal progenitors in the DG induces neurogenesis promoting cell survival, neuronal differentiation, and enhanced dendritic structural complexity. The morphological changes are paralleled by improved spatial learning and memory and hippocampus-dependent long-term memory persistence (Wang et al. 2014). The discovery that memory can be prolonged by stimulating adult neurogenesis has important implications for the development of therapeutic strategies to treat memory disorders.

Recent studies show that restoring the function of adult neurogenesis in disease models with clear cognitive dysfunction can reverse the learning deficits. Consequently, treatments directed at this cell population may have a significant impact on disease-relevant cognitive and learning phenotypes. Fragile X syndrome (FXS) is the most common cause of inherited intellectual disability and the leading monogenic cause of autism spectrum disorders. FXS is a trinucleotide repeat disorder caused by a CGG repeat expansion in FMR1, which leads to the loss of its protein product FMRP. Deletion of FMRP in neural stem cells in adult mice affects several aspects of adult hippocampal neurogenesis leading to deficits in proliferation and differentiation of newborn neurons. This is accompanied by reduced performance in hippocampus-dependent learning tasks. Importantly, in FMRP-deficient mice, restoration of FMRP expression specifically in adult neurogenic compartments can rescue these learning deficits (Guo et al. 2011). Although more studies are needed to understand whether postnatal and adult neurogenesis plays a role in the pathogenesis of intellectual disability, these data suggest that FMRP-dependent aberrant neurogenesis could potentially contribute in part to the cognitive deficits observed in Fragile X patients.

Altered neurogenesis appears to contribute to phenotypes observed in DISC1 loss-of-function models. Disrupted-in-schizophrenia 1 (DISC1) is a multifunctional scaffold protein that has been implicated as a susceptibility gene for major mental illness including schizophrenia, bipolar disorders, and autism (Chubb et al. 2008). DISC1 plays an important role in multiple stages of adult neurogenesis in the DG including proliferation, maturation, migration, and synaptic plasticity of newborn neurons. Importantly, the levels of neurogenesis correlate with the performance on specific memory tasks. The cellular phenotypes appear to be in part regulated by disruption in critical signaling pathways modulating adult neurogenesis including the AKT-mTOR, GABA, and GSK3 $\beta$  signaling pathways (Kim et al. 2009, 2012). Indeed, DISC1 has been shown to modulate the proliferation of adult hippocampal precursor cells by inhibiting GSK3 $\beta$  activity (Mao et al. 2009). Pharmacologically

targeting these pathways leads to restoration of both neurogenesis and behavioral phenotypes. Notably, in a *DISC1* loss-of-function mouse model, treatment with a GSK3 $\beta$  inhibitor, SB-216763, normalizes both the neurogenesis deficits and the schizophrenia- and depression-like behaviors (Mao et al. 2009). In another study, the downregulation of *Disc1* specifically during the development of newborn neurons results in defective neuronal maturation, neuronal hyperexcitability, and alteration of neuronal structure. On a molecular level, knockdown of *Disc1* results in increased mTOR signaling. Moreover, *Disc1* knockdown induces cognitive and affective deficits and behavioral abnormalities are reversed by pharmacological inhibition of the mTOR pathway (Zhou et al. 2013a).

The described roles of adult hippocampal neurogenesis in neurodevelopmental disorders suggest that treatments targeting the adult neural stem cell population may have a significant impact on pathophysiology and endophenotypes and can represent a novel therapeutic approach.

### 3.2 Potential of Screening for Neurogenic Compounds

Neuro-regenerative approaches aimed at treating pathological cognitive decline could include both the stimulation of endogenous adult neural stem cell populations and the transplantation of exogenous stem cells in the brain. Seminal experiments suggest that both approaches have potential for treating neurological diseases. For example, in a mouse model of hippocampal neurodegeneration that results in significant memory impairment, transplanting neural stem cells improves cognition (Yamasaki et al. 2007). Similarly, transplantation of hippocampal neural stem cells ameliorates complex cognitive deficits in a model of Alzheimer's disease characterized by abundant amyloid/TAU pathology. Interestingly, the behavioral rescue is achieved despite persistent pathological hallmarks and it is mediated by BDNF-dependent increase in hippocampal synaptic density (Blurton-Jones et al. 2009). On the other hand, the ability of neural stem cells to be reactivated in aging and in disease conditions supports the idea that identification of novel pharmacological targets/molecules promoting adult hippocampal neurogenesis represents a promising therapeutic approach.

A search of Thomas Reuter Integrity suggests that there are well over 50 relevant patents claiming neurogenic molecules. A large number of diverse chemical classes are neurogenic and have been patented for diverse CNS therapeutic indications (Rishton 2008). Reported patents claim that besides CNS acting molecules such as anticonvulsants, cognition modifiers, anxiolytics, and mood-stabilizing agents, also antidiabetic, blood pressure-lowering, and cholesterol-lowering agents have surprisingly shown neurogenic properties (Rishton 2008). For example, metformin, which is widely used to treat type II diabetes and other metabolic syndromes, has been shown to have neurogenic properties (Wang et al. 2012). In vitro work on both mouse and human cell cultures shows that metformin promotes neurogenesis and this translates in vivo in increased neurogenesis and enhanced spatial reversal learning in a water maze task.



A promising route for the identification of novel neurogenesis-increasing compounds is the high-throughput screening of chemical libraries using neural stem cell-based assays. Screens have already demonstrated the potential to elucidate known and novel mechanisms regulating adult hippocampal neurogenesis. In an early study, 1,200 compounds with known pharmacological activity were screened on rat neurospheres for proliferative and differentiation capacity leading to the identification of many CNS-relevant targets. Active compounds included modulators of dopamine, serotonin, opioid, glutamate, and vanilloid signaling (Diamandis et al. 2007). Besides targeting known receptors relevant for neurogenesis, molecule screening can help identify novel relevant signal transduction pathways associated with hippocampal plasticity and cognition. In another screen the small molecule isoxazole 9 [Isx-9; *N*-cyclopropyl-5-(thiophen-2-yl)isoxazole-3-carboxamide] was identified. Isx-9 robustly induces neuronal differentiation in an *in vitro* model of adult neural stem cells. In addition, Isx-9's effects appear to involve myocyte-enhancer factor 2 (Mef2), a family of transcription factors that had never been linked before to adult neurogenesis *in vivo* (Schneider et al. 2008). In a follow-up study, it has been shown that Isx-9 promotes multiple stages of neurogenesis *in vivo* and this correlates with enhanced memory in Morris water maze tasks (Petrik et al. 2012). The mechanism of action of Isx-9 on hippocampal neurogenesis and cognition is at least in part cell autonomous since inducible deletion of Mef2 isoforms from neural stem cells and their progeny thwarts the cognitive enhancing effect. The identification of ISX-9 highlights the potential of small molecule screening campaigns to identify novel mechanisms of action relevant to hippocampal neurogenesis and cognition.

A novel *in vivo* screening campaign has been undertaken identifying a compound called P7C3 with neurogenic properties (Pieper et al. 2010). Further characterization demonstrates that P7C3 can enhance neurogenesis in the dentate gyrus, can modulate mitochondrial physiology and neuronal survival, can increase synaptic activity, and can preserve cognitive capacity in aged rats. The target(s) and pathway(s) of P7C3 remain unknown, which provides both a challenge as well as an interesting opportunity to identify new pathways linked to neurogenesis and pathological cognitive decline. Clearly, the mechanisms mediating the effect of P7C3 on cognition might involve biological processes beyond hippocampal neurogenesis that could regulate broader aspects of brain plasticity. In follow-up studies, modified and more potent analogues of P7C3 demonstrated that the compound class exhibits neuroprotective effect in models of Parkinson's disease, amyotrophic lateral sclerosis, traumatic brain injury, and age-related cognitive decline (MacMillan et al. 2011; Blaya et al. 2014; Walker et al. 2014). Derivatives appended with immobilizing moieties may reveal the protein targets of the P7C3 class of neuroprotective compounds.

Few classes of neurologically active molecules have been discovered in the last 50 years, at least in part because neuroscience drug discovery efforts have been dominated by target-based assays. Unlike target-based approaches, phenotype-based screens can identify compounds hitting on pathways that capture the complexity of the neurobiological tissue. One impressive example of a large-scale HTS

screening campaign on primary cells has been recently reported, where one million small-molecule compounds have been screened on primary rat neurospheres, assessing proliferation and differentiation capacity based on the measurement of ATP levels (Liu et al. 2009). Over 5,000 primary hits have been identified to induce proliferation and differentiation. Further characterization of these compounds and a strategy for target identification will potentially provide novel insight into the mechanisms involved in the regulation of neural stem cells and adult neurogenesis.

As highlighted above, several neurodevelopmental disorders show adult neurogenesis alterations that appear to be partly responsible for cognitive deficits. Recent advances in human-induced pluripotent stem cell (hiPSCs) technologies allow the use of human cells with patient-specific genetic alterations for in vitro neuronal disease modeling. In vitro human neuronal differentiation recapitulates several aspects and stages of in vivo neurogenesis and this system can be used to characterize specific disease-related phenotypes observed in vivo. Moreover, hiPSCs represent an unprecedented tool for development of platforms for phenotypic screening using human tissue- and disease-relevant models. Despite the challenges associated with the novelty of the technology and the limited understanding of human neuronal differentiation in vitro, hiPSC disease models hold great promise as tools for innovative drug discovery (Chailangkarn et al. 2012; Bellin et al. 2012).

### 3.3 Translational Biomarkers of Human Neurogenesis

In CNS translational research, good translational biomarkers are crucial to identify pre-symptomatic early disease states, to improve dose finding, and to allow patient stratification and responder/nonresponders analysis, significantly affecting the success in drug development. As described above, increasing preclinical evidence in animal models of neurodevelopmental disorders, schizophrenia, Alzheimer's disease, stress, and depression demonstrates that alterations in neurogenesis correlate with behavioral and cognitive symptoms. Moreover, multiple pharmacological interventions targeting cognition modulate adult hippocampal neurogenesis. Therefore, the identification of a noninvasive biomarker for human neurogenesis is an area of growing interest and intensive scientific research. The lack of biomarker currently represents a key limitation in the ability to ultimately demonstrate the relevance of the neurogenic process in human health and disease and its role in mediating beneficial effects of therapeutic interventions.

Identification of hippocampal neurogenesis-specific biomarkers in blood or CSF could serve as a proxy for the rates of neurogenesis in the brain. Immature neuronal precursors in the adult brain are characterized by specific transcriptomes, cellular and membrane proteomes, secretomes, metabolomes, and lipidomes (Ramm et al. 2009; Knolhoff et al. 2013). Unbiased approaches to identify neurogenesis-specific transcriptomic profiles have led to the identification of several transcripts expressed during specific stages of adult neurogenesis (Miller et al. 2013; Couillard-Despres et al. 2006; Lim et al. 2006). Moreover, expression levels of

miRNA involved in the regulation of neurogenesis appear to be altered in brain samples from AD patients. Importantly, miRNA can be released and detected in the CSF, representing a potential biomarker (Cogswell et al. 2008). Similarly, some neurogenesis-specific proteins are secreted into fluids including the CSF. For example, doublecortin (DCX), which encodes for a microtubule-associated protein specifically expressed in newborn neurons, is detected in CSF of both rodents and humans (Kremer et al. 2013).

Another potential strategy to monitor neurogenesis is brain imaging. A possible approach would be to identify a PET ligand binding molecular markers of adult hippocampal neurogenesis. A PET imaging strategy could be feasible based on anatomical considerations. PET resolution is in the order of 1.5–3 mm, the hippocampus volume in human is  $\sim 3 \text{ cm}^3$ , and the dentate gyrus is  $90 \text{ mm}^3$ . It has been reported that around 0.033 % of granular cells are newborn neurons in old primates and 0.07 % in old mice (Aizawa et al. 2009). Considering the sensitivity of PET imaging, shown to reach 30 pM of receptor density for the D2 receptor, the detection of the newborn cells' fraction would be feasible (Kessler et al. 1993; Farde 1996). The challenge is to find a hippocampal neurogenesis-selective protein with a binding pocket that could serve as a PET tracer. 18F-3'-deoxy-3'-fluoro-L-thymidine (FLT) has been described to be a potential PET tracer to monitor neural stem cell division in the rat hippocampus (Rueger et al. 2010). FLT is a thymidine analogue that accumulates in dividing cells and it is a common marker to monitor cell proliferation in tumors. For measurements in the brain, strategies to improve the signal-to-noise ratio and to reduce radioactive doses would significantly implement the approach (Rueger et al. 2010). Monitoring neurogenesis targeting immature neurons could represent another approach considering that in aged macaque monkeys and mice, immature neurons are 4- to 4.5-fold more abundant than dividing NPCs (Aizawa et al. 2009).

MRI/MRS technologies could be a potential way to identify biomarkers of neurogenesis or at least epiphenomena of the process. A conceptually very appealing study, using MRI-based technologies, suggested relative cerebral blood volume (rCBV) increases specific to the dentate gyrus as a putative biomarker for neurogenesis (Pereira et al. 2007). As described previously, neurogenesis and angiogenesis in the DG are tightly linked processes (Palmer et al. 2000; Louissaint et al. 2002). However, the specificity of this method is challenged by the fact that hippocampus hemodynamics observed by fMRI is sensitive to changes due to disease states and drug treatments (Choi et al. 2006; Littlewood et al. 2006; Gozzi et al. 2008).

Using proton MRS, a very exciting study identified a particular resonance at 1.28 ppm with enhanced prevalence in NPCs in vitro (Maletic-Savatic et al. 2008; Manganas et al. 2007). This marker was demonstrated to be a translational biomarker in both rats and human subjects, and the putative NPC-specific peak strongly decreases during brain development from childhood to adulthood (Manganas et al. 2007). If confirmed, this study provides an unparalleled glimpse into the human brain with the promise to provide a truly noninvasive biomarker of adult neurogenesis. Not unexpectedly, this report has aroused a certain amount of

controversy on technical and study design aspects (Friedman 2008; Hoch et al. 2008; Jansen et al. 2008; Dong et al. 2009; Ramm et al. 2009). More studies are needed to demonstrate feasibility and practicality of this approach as a tool to investigate the role of neurogenesis in a wide variety of human brain disorders.

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## 4 Conclusions

Adult hippocampal neurogenesis is a complex process that provides an excellent example of the surprising plasticity of the mature brain. Research within the last few years has identified molecular mechanisms that regulate individual steps in neurogenesis and has highlighted its function in various neurological disorders. However, the process of translating basic knowledge into pharmacological interventions is only at the beginning. Key aspects need to be further clarified to support targeting of adult neurogenesis for the treatment of neurological and cognitive disorders in humans: (1) Can results obtained from animal models of neurological disorders be translated to humans?, (2) Can changes in neurogenesis be assessed in humans (i.e., is there a biomarker)?, (3) Is it possible to identify chemical entities or biomolecules to pharmacologically modulate neurogenesis in humans? In this chapter, we have highlighted key studies investigating the role of neurogenesis in cognitive impairment associated with physiological and disease conditions. Moreover, we have described endogenous and pharmacological factors that modulate neurogenesis and have an effect on cognitive functions. Deep understanding of several of these aspects would enable the development of drugs that target and modulate adult neurogenesis in humans to treat patients with neurological disorders.

**Acknowledgments** VC and SL are supported by the Roche Postdoctoral Fellowship Program. We thank M. Iglesias for artwork.

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