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REVIEW

Neurogenesis and antidepressant action

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Abstract

A theoretical framework is proposed to gain insight into the pathogenesis of major depressive disorder (MDD). Despite being a relatively weak argument, the neurogenesis theory is suggested to compensate for the limitations of the monoamine theory. In the adult hippocampus, neurogenesis is functionally related to regulation of the hypothalamic–pituitary–adrenal (HPA) axis, inflammatory processes, cognitive functions and other aspects that contribute to etiological factors that lead to MDD and promote recovery from MDD. Despite a lack of investigation into neurogenesis and antidepressant action, it is proposed that chronic administration of antidepressant(s) can induce the recruitment and integration of newborn neurons into the dentate gyrus and, ultimately, lead to the remission of MDD. The extant body of literature indicates that the suppression of neurogenesis per se may be associated with an impaired response to antidepressant treatment rather than with the induction of depressive-like behaviors. Moreover, recent studies have shown that increasing the survival rate and incorporation of new neurons can alleviate depressive-like behaviors and promote stress resilience. According to the neurogenic reserve hypothesis, hippocampal neurogenesis supports specific cortical functions, including executive functions, pattern separation and contextual information processing, control over the HPA axis and behavioral coping mechanisms in response to stressful situations. Therefore, hippocampal neurogenesis may be a promising biological indicator of stress resilience and antidepressant response in patients with MDD.

Keywords Antidepressant · Biological indicator · Hippocampus · Major depressive disorder (MDD) · Neurogenesis

Introduction

Due to its high prevalence, proneness to recurrence and chronicity, depressive disorder is an important public health issue worldwide (Heo et al. 2018; Kang et al. 2018; Park et al. 2015; Park et al. 2018). Hence, the World Health Organization (WHO) predicted that depressive disorder will be second only to heart disease as a cause of early death or disability by 2020 (Lopez et al. 2006). However, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, the largest prospective and randomized antidepressant trial to date, reported that only 36.8% of patients achieved remission with first-level antidepressant treatment and 40% of remittances subsequently relapsed (McGrath et al. 2008). Dr. Thomas Insel proposed next-generation treatments for mental disorders to overcome the problems and obstacles in current psychiatry. Due to several changes in the theoretical construct, from chemical imbalances to dysfunctional circuitry, methods based on endophenotypes and biomarkers, rather than only categorical diagnoses, as well as more sophisticated and individualized clinical treatments, have been proposed (Insel 2012). Thus, the link between hippocampal neurogenesis and antidepressant action needs to be discussed in terms of next-generation treatments for depressive disorders.

Hippocampal dysfunction, which is reflective of cognitive deficits and hypothalamic–pituitary–adrenal (HPA) axis hyperactivation, is exhibited by a significant subpopulation of patients with major depressive disorder (MDD) (Bremner et al. 2004; Holsboer 2000; Perera et al. 2008). Alterations in memory consolidation and HPA axis regulation have been demonstrated using hippocampal lesion studies in non-human primates (Beason-Held et al. 1999; Brooke et al. 1994). In addition, the findings of a structural magnetic resonance imaging study in patients with chronic depression indicate a positive relationship between the reduction in hippocampal volume and untreated illness. Thus, antidepressant treatment can counteract the reduction in hippocampal volume in patients with MDD (Sheline et al. 2003). In contrast, chronic

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stress is known to be the most important clinical risk factor for MDD. Hippocampal volume has been shown to be reduced by chronic stress-induced suppression of neurogenesis in the dentate gyrus, as well as dentate atrophy and neuronal death in the CA3 subfield of juvenile monkeys, adult tree shrews and rats (Coe et al. 2003; Czeh et al. 2001; Karel 1997; Pham et al. 2003). In addition, elevated levels of adrenal steroid hormone, activation of downstream N-methyl-D-aspartate (NMDA) receptors and decreased levels of brain-derived neurotrophic factor (BDNF) are mediators of chronic stress-induced hippocampal volume loss (Cameron et al. 1998; Tsankova et al. 2006). Genetic vulnerability in rodent models of opiate and alcohol abuse, medical illnesses and other predisposing factors for depression can cause the suppression of hippocampal neurogenesis (Eisch et al. 2000; Guan and Fang 2006; Nixon and Crews 2004; Saravia et al. 2004). Moreover, cell proliferation in the prefrontal cortex (PFC), which is involved in cognitive function, is suppressed by chronic stress (Czeh et al. 2007).

In a postmortem study, decreased rates of hippocampal proliferation were not evident in patients with depressive disorder (Reif et al. 2006). The learned helplessness (LH) model is induced by chronic uncontrolled stress (CUS) in some—but not all—subjects. Despite the suppression of hippocampal precursor proliferation owing to CUS, no further decrements in proliferation were exhibited by rats with LH (Shors et al. 2007; Vollmayr et al. 2003). The suppression of neurogenesis per se may be associated with an impaired response to antidepressant treatment rather than with the induction of depressive-like behaviors. Thus, the impairment of hippocampal neurogenesis is linked to depressive-like behaviors or depressive disorders (Perera et al. 2008; Tang et al. 2016).

The present review is divided into three sections targeting the functional role of hippocampal neurogenesis in animal models, neurogenesis in humans and neurogenesis and antidepressants.

Functional roles of hippocampal neurogenesis in animal models

Functional correlates of impaired hippocampal neurogenesis

By determining the behavioral phenotype produced by blocking neurogenesis and identifying cognitive tasks that activate new neurons, the functional role of newborn hippocampal neurons can be directly investigated. Alternatively, the functional role of neurogenesis can be indirectly explained by the function of the dentate gyrus (Perera et al. 2008). Ablation of the dentate gyrus by gamma-irradiation, antimitotic agents and apoptotic agents can critically hinder precursor cells from undergoing mitosis and prevent antidepressant(s) from increasing neurogenesis. However, alternative lesioning methods have also been used to model the reduction in basal neurogenesis rates (Santarelli et al. 2003; Saxe et al. 2006; Shors et al. 2001). Moreover, it has been reported that the ability of chronic administration of monoaminergic antidepressants to induce recovery is suppressed by the ablation of newborn neurons via focal irradiation of the hippocampal dentate gyrus. Thus, newborn neurons are regarded to be a critical factor in antidepressant action (Santarelli et al. 2003). Although impairments of delayed contextual fear conditioning and delayed spatial recognition in complex environments can result from blocking baseline rates of neurogenesis, the brief delay between training and testing has no impact on performance (Madsen et al. 2003; Raber et al. 2004; Shors et al. 2001; Snyder et al. 2005; Winocur et al. 2006). Decreasing basal rates of neurogenesis have not resulted in worsened performance in the novelty suppressed feeding (NSF), light–dark choice, open field, passive avoidance, or elevated plus-maze tests, which are all used to evaluate the efficacy of antidepressants (Santarelli et al. 2003; Saxe et al. 2006; Raber et al. 2004). Hence, it has been suggested that it is not affective—but cognitive—tasks that involve more complex environments and increased cognitive demands due to the prolonged delays between training and testing, which require neurogenesis (Winocur et al. 2006).

After immuno-labeling the brain for expression of stimulus-specific immediate early genes, newborn neurons were found to be activated and recruited into the synaptic circuitry by re-exposure to an enriched environment and the spatial memory task. Conversely, completely different environments or excessively brief intervals between training and testing provoked no activation (Kee et al. 2007; Tashiro et al. 2007). Because recruitment over extant mature granule cells is evident in newborn neurons ($\geq$4 weeks) due to their possibly higher plasticity, impairment in spatial cognitive function has been demonstrated by the disruption of neurogenesis, in which testing is delayed by approximately four weeks (Snyder et al. 2005). Hence, it has been suggested that short-term retention between dissimilar settings is mediated by mature neurons, whereas delayed retention within contextually similar environments is mediated by newborn neurons.

Moreover, place recognition occurs in granule cell neurons in the dentate gyrus in a manner analogous to pyramidal place cells in the CA3 region. The memory-like internal spatial representations of the external environment are formed by the firing patterns of place cells. Remapping of place cells is caused by changes in the environmental context. The switching on and off of different clusters of pyramidal cells is involved in the remapping of the CA3 region. In addition, granule cells do not have the ability to switch on and off and the changes in coordinated firing patterns reflect remapping in the dentate gyrus. For environments that are sufficiently distinct to result in remapping of the CA3, the firing patterns of

dentate cells are not altered. However, the firing patterns of dentate cells are changed by subtle alterations to the environment that do not cause CA3 remapping (Perera et al. 2008). Hence, it is not the changes across different contextual frameworks but the subtle changes within the same environmental context in the dentate cell responses. Segregation, which is the cognitive process that differentiates between relevant and irrelevant environmental stimuli and is uniquely dependent on the dentate gyrus, may contribute to the ability to detect subtle changes within an otherwise similar environment (Olypher et al. 2006). Thus, it is possible that linking temporally separated events that involve subtle or novel changes within a contextually similar setting requires neurogenesis.

Neurogenic reserve, executive functions and pattern separation

The functions of dentate gyrus neurogenesis include providing a neurogenic reserve, performing executive functions, determining pattern separation, providing spatial/contextual memory, regulating the HPA axis and coping with stressful situations (Tanti and Belzung 2013). The neurogenic reserve hypothesis posits that increased hippocampal genesis can enhance the adaptability to a challenging environment in lower plastic situations, such as older age (Kempermann 2008). According to this hypothesis, improved coping abilities in stressful situations at older ages and better resiliency during confrontations with environmental stressors are the results of newborn neurons generated throughout life. Thus, it is possible that the generation of newborn cells that compensate for a loss in neural reserve may be promoted by antidepressant treatments (Tanti and Belzung 2013). Additionally, in accordance with cognitive neuroscience, executive functions include aspects of inhibition, task shifting and updating (Miyake et al. 2000). In the reciprocal direct and indirect connection between the PFC and the hippocampus, the hippocampus is critically involved in executive dysfunction in MDD. Consistent with this framework, hippocampal volume is correlated with executive dysfunction in patients with depression (Frodl et al. 2006; Godsil et al. 2013; Laroche et al. 2000). Moreover, based on the relationship between decreased executive functions and the non-responsiveness to fluoxetine in MDD, it is possible that this decreased executive performance is induced by deficits in hippocampal neurogenesis (Dunkin et al. 2000).

Moreover, it is possible that pattern separation (the ability to discriminate similar experiences and transform identical memories into non-overlapping representations) can be achieved under the influence of hippocampal neurogenesis (Leutgeb et al. 2007). However, the relationship between pattern separation and depression/effects of antidepressant treatment is unclear. Thus, further studies are needed to investigate the effects of stress, depression and antidepressants on pattern separation (Tanti and Belzung 2013). Moreover, in terms of the involvement of the hippocampus in declarative memory contextual information processing, hippocampal neurogenesis suppresses the worsening of contextual information processing in the Morris water maze, the Barnes maze and associative learning, whereas activation of newborn hippocampal neurons is preferentially exhibited during spatial or contextual tasks (Deng et al. 2009; Dupret et al. 2009; Farioli-Vecchioli et al. 2008; Shors et al. 2001; Tanti and Belzung 2013). These findings are consistent with the ability of chronic stress to impair performance in the hippocampus-dependent learning task and to induce a shift from spatial-based strategies to cue-based strategies in animal models of depression (Conrad 2010). Thus, it is possible that a shift from the habit-based strategies associated with chronic stress and major depression to more flexible and chronic strategies may be induced by the increased number of newborn hippocampal neurons. Additionally, with the increased number of the new cells, performance in declarative memory increases and recovery from depressive-like behaviors is elicited (Tanti and Belzung 2013).

Neurogenesis and HPA axis regulation

Normal HPA function can be compromised by the ablation of neurogenesis. When neurogenesis is blocked, more time is required to return to pre-stress levels of corticosterone and the HPA axis is bluntly regulated (Snyder et al. 2011). In addition, a decrease in negative regulation of the HPA axis and an increase in positive regulation of the HPA axis have been hypothesized to represent the compromise of PFC inhibition and amygdala hyperactivation, respectively (McEwen 2002). Antidepressants can facilitate the recruitment of new neurons and compensate for the loss of function related to alterations in brain areas participating in the regulation of the HPA axis. Moreover, the synapses of CA3 pyramidal cells are established and the process leading to the release of glucocorticoids is inhibited through multi-synaptic projections to relay to areas including the lateral septum, the bed nucleus of stria terminalis and other nuclei of the hypothalamus (Surget et al. 2008). Furthermore, it is known that the basolateral nucleus of the amygdala has an effect on neurogenesis and the loss of anxiety behaviors. The regulation of the activity pattern of new hippocampal neurons is affected by the activity of the basolateral amygdala. Thus, the recruitment of new hippocampal neurons in a contextual fear conditioning task is blocked by lesions in the basolateral amygdala (Kirby et al. 2012; Boku et al. 2018). Chronic antidepressant treatment can reverse high anxiety behavior by preventing the anxiety associated with depressive symptomatology (Souery et al. 2007). In addition, modified anxiety-like behavior is elicited by specific lesioning in the ventral subregion of the hippocampus in the novelty suppression of feeding, exposure to predator-related stimuli, elevated plus maze and tone fear conditions

(Bannerman et al. 2002; Blanchard et al. 2005; Burns et al. 1996; Degroot and Treit 2004; Hunsaker and Kesner 2008; Maren and Holt 2004; Trivedi and Coover 2004).

Relationship between neurogenesis and MDD

Regarding the impact of new hippocampal neurons in affective disorders, neurogenesis may be involved in the precipitation of a depressive episode and in recovery after therapy (Tanti and Belzung 2013). Additionally, potential links between neurogenesis and antidepressant resistance (Khemissi et al. 2014) and between neurogenesis and stress resilience (Culig et al. 2017) have been investigated. Despite discrepancies in the extant body of literature, there is some consensus that the suppression of neurogenesis in mice acts by negatively affecting the antidepressant response, rather than inducing depressive behavior (Khemissi et al. 2014; Li et al. 2017; Nollet et al. 2012). Recent studies using genetic models to manipulate the activity of new neurons or increase neurogenesis tend to suggest that resilience to stress may be promoted and depressive-like behaviors may be alleviated by increasing the survival rate and incorporation of new neurons (Anacker et al. 2018; Appel et al. 2018). However, a postmortem study showed that hippocampal progenitor cells do not respond to antidepressant(s) in elderly depressed patients (Lucassen et al. 2010).

Neurogenesis suppressed by stress or noxious stimuli can cause the recruitment of extant mature neurons to represent both novel and old stimuli and result in the impairment of segregation of irrelevant, old stimuli from relevant novel stimuli. The detection of new, subtle contextual changes is impaired by interference with the encoding of novel stimuli and results in the uncoupling of affect from external context and the prevention of recognition of the eventual reduction or cessation of stress. Despite the cessation of the triggering stressor, Perera et al. (2008) found that depressed mood is unremitting and persistent. In addition, the cognitive distortion that triggers core symptoms of major depression can be induced by the uncoupling of affect from external reality. Hence, it is possible that the pathological state of depressive disorder can be determined by the emotional state at the time of neural suppression. It is also possible that uncoupling during depressed mood and chronic anxiety can result in depressive disorder and anxiety disorder, respectively (Bremner and Vermetten 2004; Clewell 2004; Perera et al. 2008). Moreover, it has been proposed that increasing or decreasing the integration of new neurons in the neuronal network of the adult hippocampus may have a significant role in modulating cognition and emotion (Baptista and Andrade 2018). In terms of animal models of MDD, it has been suggested that the reduction of interference between overlapping memories through pattern separation may be triggered by the impairment of adult neurogenesis in the dentate gyrus. Based on the computation model, it has been shown that higher memory accuracy can be linked to adult neurogenesis, whereas impairment in memories stored in a depressive state can be linked to disturbances in adult neurogenesis. In addition, it has been suggested that a later depressive episode can impair the memories stored in an earlier, asymptomatic state; this retrograde effect is exacerbated by the depressive episode. Thus, it has been concluded that episodic memory deficits in MDD may be triggered by cognitive retrieval biases that are associated with the impairment of adult neurogenesis (Fang et al. 2018). Moreover, it has been suggested that a negative mood state associated with uncoupling emotions from the external context can be triggered by stress-induced impairment in adult neurogenesis. Hence, negative mood without the initial stressor can persist in MDD (Perera et al. 2008).

Hippocampal atrophy has been proposed to be a trait marker of MDD (Perera et al. 2008). In addition, it has been reported that greater hippocampal volume reduction is observed in depressed patients with a history of early trauma (Vythilingam et al. 2002). Moreover, the interactions between early life stress and abnormal genotypes, including a short allele of the promoter for the serotonin transporter and a val66met genotype of the *BDNF* gene, have been suggested as trait markers for MDD (Kaufman et al. 2006). It has been shown that excessive cortisol levels during stress are associated with the gene through environmental interactions and that hippocampal neurogenesis is suppressed by high cortisol levels in primates (Bennet et al. 2002; Coe et al. 2003). Thus, an uncoupling of affect from context results from the stress-induced reduction of neurogenesis levels below a critical level. In the elderly, hippocampal volume reduction is not regarded to be a predictive factor for the severity of depression. This is in contrast with what is observed in younger adults, although suppressed hippocampal neurogenesis and hippocampal volume loss result from aging (Karel 1997; Manganas et al. 2007; Sheline et al. 2003). In addition, in older animals, increased glucocorticoid activity and decreased BDNF expression can result in decreased neurogenesis (Cameron and McKay 1999; Hattiangady et al. 2005; Leuner et al. 2007). Only in younger rats is cognitive performance impaired by age-related decreases in neurogenesis, whereas in older animals, stimulation of neurogenesis may increase cognitive impairment (Bizon et al. 2004; Cameron and McKay 1999; van Praag et al. 2005). Moreover, a preliminary study has shown that in older rats, neurogenesis is not stimulated by antidepressants, although antidepressants reflect therapeutic efficacy (Perera et al. 2008). In rodent models, neurogenesis is suppressed by medical illnesses via pro-inflammatory cytokines, infectious lipopolysaccharides and β-amyloid deposits (Guan and Fang 2006; Monje et al. 2003; Zhang et al. 2007). Hence, it is possible that depression in the elderly cannot be explained solely by neurogenesis.

The neurogenesis hypothesis

The neurogenesis hypothesis posits that impairment in adult hippocampal neurogenesis triggers MDD and, thus, has the potential to explain the lag in antidepressant action. One mouse model demonstrated that delayed antidepressant efficacy may be associated with the maturation of immature hyperplastic neurons that are preferentially recruited for dentate synaptic activity (Jessberger and Kempermann 2003). With antidepressant treatment, a function related to new hippocampal cells is facilitated, their incorporation into the corresponding functional network(s) is improved and their maturation and survival are increased (Tanti and Belzung 2013). Moreover, the speed of maturation can be accelerated by antidepressants and even more so by convulsive treatments including electroconvulsive therapy (ECT) (Overstreet-Wadiche and Westbrook 2006; Segman et al. 1995). In addition, it has been reported that instantaneous responses in severely depressed patients are generated by deep brain stimulation (Johansen-Berg et al. 2008). It has been suggested that mechanisms other than dentate gyrus neurogenesis, including dendrite arborization in mature hippocampal neurons and activity within the subregions of the PFC, can explain these rapid antidepressive effects (Bremner et al. 2004; McEwen and Chattarji 2004). Delayed improvements are associated with hippocampus-dependent cognition and are predictive of endurable remission, whereas the acute response is transient and associated with relapse (Deuschle et al. 2004). Hence, although there are several controversies and debates regarding the possible functional and clinical roles for adult hippocampal neurogenesis, it can be concluded that delayed antidepressant effects associated with hippocampus-dependent cognitive improvements and remission of depressive symptoms—not acute responses—are mediated by neurogenesis (Santarelli et al. 2003; Snyder et al. 2005; Wang et al. 2008; Baptista and Andrade 2018).

Neurogenesis in humans

Functional implications of adult human hippocampal neurogenesis in MDD

Although the functional implications of adult human hippocampal neurogenesis remain unclear, it is speculated that memory formation and consolidation can be functionally associated with hippocampal neurogenesis and mood disorders can be involved in dysfunctional neurogenic patterns (Apple et al. 2017). In terms of the correlation between depression and neurogenesis in humans, decreased hippocampal volume has been exhibited by patients with MDD compared with healthy controls in several magnetic resonance imaging studies (Sheline et al. 1996; Bremner et al. 2000; Videbech and Ravnkilde 2004). In addition, more tightly packed densities of glia and granule cell neurons in the hippocampus have been exhibited by patients with MDD in postmortem studies (Stockmeier et al. 2004). It is believed that the decline in adult neurogenesis is correlated with depression in humans (Micheli et al. 2018); however, debate as to the nature of the correlation between neurogenesis and depression is ongoing. One study found that a decreased turnover within hippocampal circuits, rather than a decrease in overall neuron number, may influence hippocampal function (Czeh and Lucassen 2007). Conversely, an increased volume of the left hippocampus is exhibited by patients with depression treated with antidepressants (including fluoxetine) for <3 years and is associated with a better treatment outcome compared to those with smaller hippocampal volume (Frodl et al. 2008). In terms of physical exercise, its efficacy in the treatment of depression has been supported by several studies (Craft and Perna 2004; Schuch et al. 2016). A single-blind randomized trial involving older adults reported that a 2% increase in volume in the anterior hippocampus was caused by aerobic exercise and corresponded to loss occurring every 1 to 2 years with age-induced improvements in spatial memory (Eriksson et al. 2011). Additionally, cognitive function has been found to improve with exercise in patients with Alzheimer's disease (Kemoun et al. 2010). However, chronic exercise intervention-induced increases in the resting concentrations of blood BDNF were not evidenced in a recent meta-analysis that included six studies in patients with MDD. Thus, a definitive conclusion cannot be drawn in terms of exercise-induced neurogenesis in depression (Dinoff et al. 2018). Despite the controversies, structural changes in the brain may be induced by exercise and associated with protection against age-related neuronal loss and functional decline (Micheli et al. 2018).

Adult neurogenesis in humans versus rodents

Findings for adult human neurogenesis are scarce, whereas rodent models have been extensively used in studies investigating neural stem cells (Apple et al. 2017). Adult human neurogenesis in the subgranular zone of the dentate gyrus was first presented in the findings of a study by Eriksson et al. (1998). The authors found bromodeoxyuridine (BrdU) incorporation within the DNA of dividing cells of the hippocampus, which are morphologically indistinguishable from adult-born hippocampal neurons in rodent models. This has been demonstrated in postmortem brain immunohistochemical analyses of terminally ill cancer patients with BrdU injection. Thus, this strong evidence has supported adult human neurogenesis. Based on a net loss in the dentate gyrus throughout adulthood, it can be suggested that neuronal volume loss is delayed rather than arrested throughout adulthood by continued neurogenesis (Spalding et al. 2013). Moreover,

in studies investigating the human ventricular-subventricular zone (V-SVZ) and olfactory bulb, compared with rodent models, cytoarchitecturally distinctive V-SVZ niche organization and neuroblast migration in humans have been described in several studies (Bergmann et al. 2012; Ernst et al. 2014; Sanai et al. 2011). A dense ribbon of astrocytes, after the subependymal gap, has been found in the V-SVZ in humans (Sanai et al. 2004). Due to their multipotency, neurons, astrocytes and oligodendrocytes can be generated by this ribbon of astrocytes (Sanai et al. 2011). Despite the strong germinal capacity of these putative neural stem cells in vitro, their migratory route differs between rodents and humans. Based on the findings of Sanai et al. (2011), it has been demonstrated that olfactory neurogenesis in humans develops only during the first 18 months of life and dramatically declines by 24 months of age. Thus, it has been proposed that neurogenesis in the olfactory bulb is essentially absent in human adult tissue (Sanai et al. 2004; Sanai et al. 2011). However, it has been argued that, in humans, hippocampal neurogenesis may drop very sharply with age and the maturation of new neurons possibly takes significantly longer. An autoptic study involving healthy human subjects between 14 and 79 years of age suggested that human-specific cognitive functions are sustained by ongoing hippocampal neurogenesis throughout life and that altered cognitive-emotional resilience may be linked to the decline in hippocampal neurogenesis (Boldrini et al. 2018; Charvet and Finlay 2018).

Instead of inducing new neurons in the olfactory bulb, the migration of neuroblasts from the V-SVZ to the striatum in humans has been proposed a functionally distinct mechanism for the V-SVZ compared with rodent models (Ernst et al. 2014). It is known that not only motor function but also cognitive flexibility, is functionally associated mainly with the striatum (Ernst and Frisen 2015). Since it was described that new neurons in the striatum can be produced by subpopulations of astrocytes in this region, it has been proposed that an inherent capacity to regenerate neurons, independent of the neighboring neurogenic cells in the V-SVZ, is possessed by the striatum (Magnusson et al. 2014). Thus, neurodegenerative diseases with prominent striatal involvement have been the focus of studies investigating striatum-specific neuronal turnover.

Neurogenesis and antidepressants

Neurogenesis and its stimulation

Adult neurogenesis consists of separate multistep processes, including proliferation of neural progenitors, differentiation of cell types into neuronal or glial cells, maturation, including migration, neurite extension, synaptic branching, functional advancing and circuit integration and survival (Eliwa et al. 2017; Kempermann et al. 2015). Neurogenesis in the dentate gyrus of adult rodents and non-human primates is stimulated by most antidepressants, including tricyclic antidepressants (TCAs), selective serotonin-reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs) and ECT (Czeh et al. 2001; Perera et al. 2007; Li et al. 2004; Madsen et al. 2003 ; Malberg et al. 2000). More specifically, with chronic antidepressant administration, neural progenitor proliferation is stimulated, maturational processing is accelerated and survival of newborn hippocampal cells is promoted in animal models, including rodents and primates (Perera et al. 2011; Wang et al. 2008; Zhao et al. 2008). Neurogenesis is also stimulated by psychotropic agents with antidepressive properties, including mood stabilizers and atypical antipsychotics and interventions against depression including exercise, environmental enrichment and hippocampal learning (Kodama et al. 2004; Manji et al. 2000). Moreover, other drugs eliciting antidepressant-like effects, including tianeptine, corticotropin-releasing factor-1, or vasopressin V_{1b} receptor antagonists, glutamatergic agents, endocannabinoid ligands and melanin-concentrating hormone antagonists, elicit pro-neurogenic actions with beneficial effects in the treatment of depressive-like states in animal models (Alonso et al. 2004; Czeh et al. 2001; David et al. 2007; Jiang et al. 2005; Yoshimizu and Chaki 2004). However, other psychotropic agents without antidepressive properties, such as haloperidol and benzodiazepines, have no impact on neurogenesis (Malberg et al. 2000; Santarelli et al. 2003). It has been proposed that there is a causal relationship between hippocampal neurogenesis and the therapeutic efficacy of antidepressants (Mahar et al. 2014). In addition, it has been suggested that all effective depression treatments increase the number of newborn neurons in the hippocampus in adulthood (Tanti and Belzung 2013). However, although the administration of almorexant (a dual orexin receptor antagonist) results in the restoration of behavioral alterations associated with chronic stress and normalization of the HPA axis, it provokes a decrease in cell proliferation and neurogenesis in the ventral hippocampus (Nollet et al. 2012). Thus, the link between hippocampal neurogenesis and the therapeutic actions of antidepressants tends to be proportional; however, findings have been somewhat contradictory.

Antidepressant-triggered neurogenesis

A legion of studies investigating serotonergic neurons of the raphe nuclei, along with pharmacological and knockout/knockdown studies, have revealed that specific components of the serotonergic system play key roles in producing the neurogenic effects of antidepressants (Alenina and Klempin

2015; Banasr et al. 2004; Mahar et al. 2014). The proliferation of neural progenitors and the survival of adult-born neurons are positively correlated with serotonin levels, which is mediated via direct actions on 5-hydroxytryptamine (5-HT)$_{1A}$, 5-HT$_2$ and 5-HT$_4$ receptors (Klempin et al. 2010; Samuels et al. 2016). Moreover, because of its direct effect on hippocampal neurogenesis, the norepinephrine system is also regarded to be a factor involved in the neurogenic effects of antidepressants (Santarelli et al. 2003). Remarkably, the multistep processes of hippocampal neurogenesis, including proliferation, maturation and survival, are positively regulated by the serotonergic system, whereas only the early stages of adult neurogenesis are regulated by the norepinephrine system (Kulkarni et al. 2002). Furthermore, the therapeutic effect of antidepressants is mediated by signaling pathways, including the cyclic adenosine monophosphate-response (cAMP)-phosphate kinase A (PKA)-cAMP element-binding protein (CREB) pathway, the Ras-mitogen-activated kinase A (PKA)-CREB pathway, the phospholipase Cγ (PLCγ)-Ca^{2+} pathway and the phosphatidyl inositol-3 kinase (PI3K)-Akt (serine threonine kinase or protein kinase B) pathway (Eliwa et al. 2017). Above all, a final common molecular pathway, which involves the cAMP-PKA-CREB pathway, including monoamine release, serotonin (5-HT$_{1A}$) receptor activation, intracellular phosphorylation of CREB (pCREB) and expression of BDNF and binding of BDNF to the tyrosine kinase B (TrkB) receptor, is up-regulated (Brezun and Daszuta 2000; Malberg and Blendy 2005; Sairanen et al. 2005; Santarelli et al. 2003; Schmidt and Duman 2007) (Fig. 1). A close link has been proposed between the facilitation of BDNF-TrkB signaling and the therapeutic effects of antidepressants. The activity-dependent reorganization of neuronal connections in response to environmental stimuli is facilitated by antidepressant-induced plasticity. The rapid effect of ketamine intervention in alleviating depressive symptoms can, at least, be partially mediated by the activation of TrkB receptors and consequent changes in structural plasticity (Rantamäki 2017). In addition, the expressions of diverse genes that up-regulate vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), insulin-like growth factor (IGF) and other factors are increased with the antidepressant-mediated induction of neurogenesis (Khawaja et al. 2004; Newton et al. 2003; Perera et al. 2007). During a two- to four-week period that corresponds to the therapeutic delay in the pharmacological treatment of depressive disorders, the proliferation, maturation and functional activation of newborn granule cell neurons are induced by antidepressants (Esposito et al. 2005; Perera et al. 2008). The mitotic effects of antidepressants have been observed in subregions of the PFC and in the CA3 subfields of the hippocampus; however, these effects have not been observed in the subventricular zone (SVZ) (Perera et al. 2007; Malberg et al. 2000; Santarelli et al. 2003).

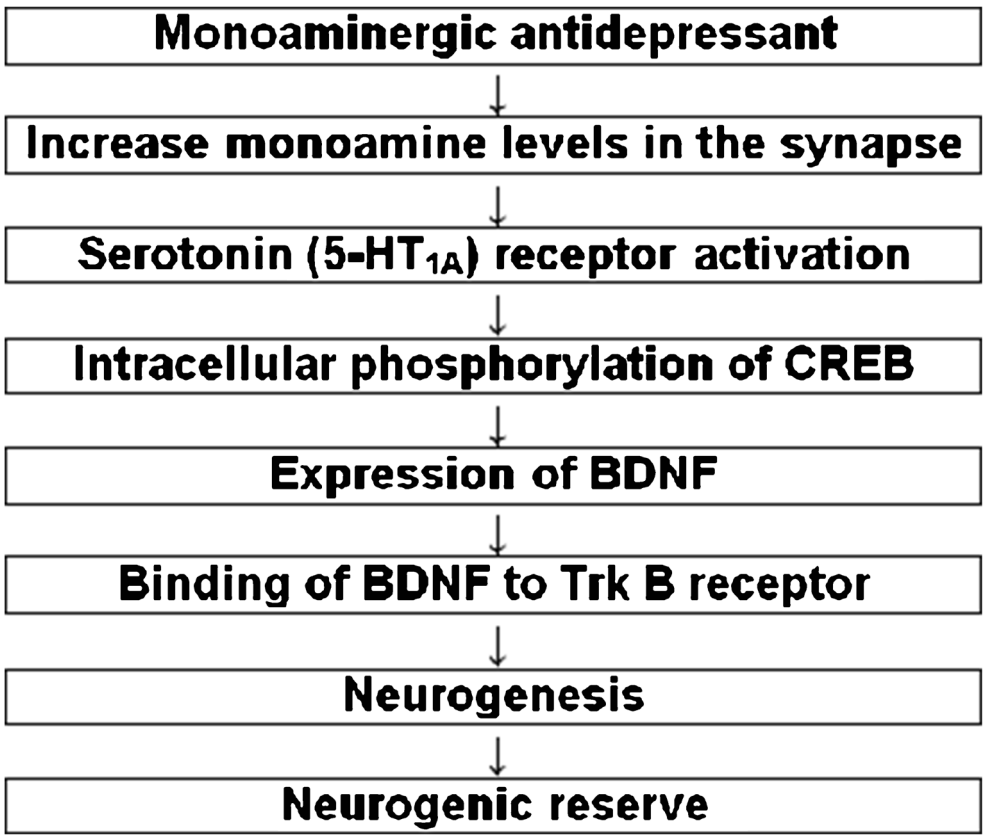

Fig. 1 A potential pathway for the relationship between antidepressant action and neurogenesis. BDNF, brain-derived neurotrophic factor; CREB, cyclic adenosine monophosphate-response element-binding protein; Trk, tyrosine kinase

In tree shrews treated with tianeptine, the increase in the rate of hippocampal neurogenesis is coupled with a reversed stress-induced cortisol response (Czeh et al. 2001). However, it has been shown that not only antidepressants but also anxiolytics lacking antidepressive properties, can reverse the stress-induced cortisol response (Nixon and Crews 2004). Because anxiolytics lacking antidepressive properties have no significant influence on neurogenesis, antidepressant efficacy cannot be fully modeled based on the stress-induced cortisol response. In mice, knockout of the 5-HT_{1A} receptor, as well as use of the CUS paradigm, result in the blockade of neurogenesis and the loss of antidepressant efficacy (Santarelli et al. 2003; Wang et al. 2008). Conversely, ablating neurogenesis has not been shown to prevent environmental enrichment from improving performance on the NSF test in the same strain of mice (Meshi et al. 2006). Beyond debates regarding the complex relationship between adult neurogenesis and antidepressant efficacy, we may speculate that neurogenesis is associated with the delayed effect of antidepressants in the CUS model, whereas it is less critical as far as the effect of antidepressants in the NSF test is concerned (Santarelli et al. 2003). The model for depression in the CUS paradigm can be applied to not only rodents without detailed affective variability but also to non-human primates with a wide range of affect-driven behavior (Perera et al. 2008).

In addition, the impact of regional specificity of depression models and antidepressant treatments on hippocampal neurogenesis has been examined in several studies. Remarkably, it has been consistently reported that only the more ventral portions of the hippocampus are affected by depression. Thus, it is believed that depression causes functional alterations in the ventral portions of the hippocampus. It is known that newborn neurons in this subregion may interfere with the activity of the ventral hippocampus with a pattern of input/output. The contribution of adult-born neurons in the dorsal and ventral hippocampus to memory acquisition and recall in the context of fear memory has been investigated using a Nestin-$CreER^{T2}$ mouse line. Study findings have suggested that the significant contribution to hippocampal function may be from adult-born neurons (Huckleberry et al. 2018). Conversely, chronic treatment with monoaminergic antidepressants increased the number of newborn neurons, not only in the ventral subregion but also in the dorsal subregion in animal models. However, agomelatine (a non-monoaminergic antidepressant) increases neurogenesis only in the ventral subregion of the hippocampus (O'Leary and Cryan 2014; Tanti and Belzung 2013).

Conclusions

The neurogenesis theory can compensate for limitations in the monoamine theory of MDD. In terms of antidepressant modalities, the cAMP-PKA-CREB pathway, including pCREB and BDNF-TrkB receptor binding, has been proposed to be a common final molecular pathway. The suppression of neurogenesis can result in an impaired response to antidepressants in MDD via an uncoupling of affect from the environmental context. Alternatively, antidepressant-mediated induction of neurogenesis can result in remission from depression and reduced impairment in antidepressant response to the restoration of coupling. Hence, hippocampal neurogenesis is causally involved in the remission achieved by chronic administration of monoaminergic antidepressants. Despite the poor understanding of the cognitive and biological mechanisms underlying the relationship between hippocampal neurogenesis and antidepressant treatment in current research, it is speculated that the integration of new hippocampal neurons into the dentate gyrus crucially contributes to remission under the chronic administration of antidepressants. Furthermore, consistent with the neurogenic reserve hypothesis, hippocampal neurogenesis is functionally related to spatial navigation, pattern separation, processing of contextual information, executive function, anxiety behavior and regulation of the HPA axis. Moreover, neurogenesis indices have been proposed as a potential biological indicator of stress resilience and antidepressant response in MDD. Because of the highly distinct connection patterns in the dorsal and ventral subregions of the hippocampus, some remarkable insights have been provided by the impact of models of depression and antidepressants on dorsal or ventral subregions of the hippocampus. With current advances in research methodologies, the relationship between hippocampal neurogenesis and antidepressants can be examined both clinically, through in vivo neuroimaging of neurogenesis, or pre-clinically using specifically targeted cognitive tests.

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