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DOI

[10.1016/B978-0-12-801977-1.00008-8](https://doi.org/10.1016/B978-0-12-801977-1.00008-8)

Publication date

2016

Document Version

Final published version

Published in

Adult neurogenesis in the hippocampus: health, psychopathology, and brain disease

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Citation for published version (APA):

Lucassen, P. J., Oomen, C. A., Schouten, M., Encinas, J. M., & Fitzsimons, C. P. (2016). Adult Neurogenesis, Chronic Stress and Depression. In J. J. Canales (Ed.), *Adult neurogenesis in the hippocampus: health, psychopathology, and brain disease* (pp. 177-206). Academic Press. <https://doi.org/10.1016/B978-0-12-801977-1.00008-8>

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Adult Neurogenesis, Chronic Stress and Depression

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INTRODUCTION

Stress occurs whenever an endogenous or exogenous challenge is perceived as unpleasant, aversive, or threatening for the homeostasis or survival of an individual. Following exposure to stress, various sensory and cognitive signals that trigger specific processes in the body and brain converge, helping the individual to suppress several ongoing processes and refocus attention to cope with the stressor. Even though stress is often considered a “modern disease,” the stress response itself occurs in many organisms and has been conserved throughout evolution. It enables individuals to adapt to challenges in their environment and regain homeostasis.

Stress is a very broad term and no single entity. Stress can be psychological in nature and, e.g., be triggered by interpersonal or financial

problems or result from a loss of control or unpredictability considering the outcome of a given situation (Ursin & Eriksen, 2004). Also, more biological challenges such as blood loss, dehydration or inflammation, elicit stress responses. Stress can further be acute (e.g., when facing a predator) or chronic (living in poverty or in a broken family). Important elements that determine the nature and impact of a stressor are its (un)predictability, (un)controllability, intensity, and the context in which stress occurs. The perception and interpretation of a stressor, as well as the magnitude and duration of an individual's response to a given stressor, depend largely on his/her genetic background, sex, personality, and early life history (Joels, Karst, Krugers, & Lucassen, 2007; Joels, Sarabdjitsingh, Karst, 2012; Kim et al., 2013; Koolhaas et al., 2011; Lucassen, Fitzsimons, et al., 2013; Lucassen, Naninck, et al., 2013).

The physiological responses to stress can be divided into a fast and a more delayed response. In the classic neuroendocrine stress circuit, several limbic and hypothalamic brain regions integrate a variety of inputs, and together determine the magnitude and specificity of the behavioral, neural, and hormonal responses of the individual to a particular stressor (Joels & Baram, 2009; Joels et al., 2012).

The first phase of the stress response involves a rapid activation of the autonomic nervous system that causes epinephrine and norepinephrine release from the adrenal medulla. These hormones quickly elevate basal metabolic rate, blood pressure, and respiration in seconds to minutes and increase blood flow to the organs essential for the "fight-or-flight" response, such as heart, lungs, and muscles.

The second, slower response to stress involves activation of the hypothalamic–pituitary–adrenal (HPA) axis that controls the release of glucocorticoid (GC) hormones (corticosterone in rodents and cortisol in humans) from the adrenal cortex. As transcriptional regulators, GCs generally act in a slow, genomic manner, but faster GC actions have also been described (Joels et al., 2012). Furthermore, other signaling pathways, such as the gonadal axis and the metabolic and immune system, act in concert with the HPA axis and together they help to redirect energy resources such that attention can be focused on the most urgent and important elements, whereas "maintenance" functions like food digestion or reproduction are temporarily suppressed.

Activation of the HPA axis is triggered by corticotropin-releasing hormone (CRH) in the paraventricular nucleus (PVN) that in turn induces adrenocorticotropin hormone (ACTH) release from the pituitary, which causes the release of GCs from the adrenal. Regulation occurs through negative feedback of GCs that bind to the high-affinity mineralocorticoid receptor (MR) and lower affinity glucocorticoid receptors (GR) (de Kloet, Joëls, & Holsboer, 2005). The GR helps to maintain GC levels within physiological limits (Erdmann, Berger, & Schütz, 2008; de Kloet et al., 2005; Kretz, Reichardt, Schütz, & Bock, 1999) and aberrant GR expression has, e.g., been

implicated in hypercortisolism, stress resistance, anxiety, and depression (de Kloet et al., 2005; Ridder et al., 2005; Wei et al., 2007). Furthermore, GC plasma levels are under strict circadian and ultradian control (Liston et al., 2013; Qian, Droste, Lightman, Reul, & Linthorst, 2012) and together with GR and MR function determine an individual's sensitivity and responsiveness to stress (Harris, Holmes, de Kloet, Chapman, & Seckl, 2013; Medina et al., 2013; Pruessner et al., 2010; Sousa, Cerqueira, & Almeida, 2008).

On their release in the periphery, GCs affect numerous important functions such as energy, inflammation, and lipid metabolism, among others. Thus, an imbalance in stress hormone regulation can have deleterious consequences, particularly for the brain, where GCs modulate memory, fear, and attention (de Kloet et al., 2005). Whereas acute stress is generally adaptive, chronic stress may alter the MR/GR balance (Harris et al., 2013; de Kloet et al., 2005; Qi et al., 2013) or HPA feedback and result in (prolonged) overexposure of the brain and body to stress hormones, and thus to changes in many of the functions, processes, and behaviors affected by GCs as noted above.

The abundant presence of GRs, particularly in the hippocampus, makes this brain structure very sensitive to stress (de Kloet et al., 2005; Lucassen et al., 2014; Swaab, Bao, & Lucassen, 2005; Wang et al., 2013). GRs have considerable genetic diversity in humans and changes in MR and GR (variants) have been implicated in stress disorders such as major depression disorder (MDD), in stress responsiveness and in the associated reductions in hippocampal volume (Alt et al., 2010; Czéh & Lucassen, 2007; Klok, Alt, et al., 2011; Klok, Giltay, et al., 2011; Medina et al., 2013; Qi et al., 2013; Ridder et al., 2005; Sapolsky, 2000; Sinclair, Tsai, Woon, & Weickert, 2011; Spijker et al., 2011; Vinkers et al., 2014; Wang, Joëls, Swaab, & Lucassen, 2012). In functional terms, chronic stress has been associated with reductions in hippocampal excitability, long-term potentiation, and hippocampal memory, but positive effects that depend on the timing, type, and controllability of a stressor have also been described (Joels et al., 2007, 2012). Morphological consequences of chronic stress commonly include hippocampal volume reductions, dendritic atrophy, and reductions in neurogenesis (for a review, see Lucassen et al., 2014, and references therein).

STRESS-RELATED CHANGES IN MAJOR DEPRESSION

Stress is one of the most common risk factors for the development of mood disorders such as MDD, which is thought to result from interactions between genetic predispositions and environmental interactions (Karg, Burmeister, Shedden, & Sen, 2011; Risch et al., 2009). Especially stressful life events experienced during early childhood or adolescence can program plasticity and increase the risk for MDD (Bilbo & Schwarz, 2009;

Bland et al., 2010; Boku et al., 2014; Brunson et al., 2005; Co et al., 2003; Heim, Newport, Mletzko, Miller, & Nemeroff, 2008; Koehl, van der Veen, Gonzales, Piazza, & Abrous, 2012; Korosi et al., 2012; Leuner, 2010; Lucassen, Naninck, et al., 2013; Mirescu, Peters, & Gould, 2004; Risch et al., 2009). Indeed, in a large proportion of depressed patients, the HPA axis activation and GC feedback resistance are common, as reflected by the high percentage of dexamethasone nonsuppressors in this population, hypertrophy of the adrenals and pituitary, increased plasma levels of cortisol, and increases in CRH and AVP expression in the PVN (Lucassen et al., 2014; Raadsheer et al., 1995; Swaab et al., 2005). Notably, depressed subjects show a remarkable heterogeneity in neuroendocrine function and the proportion of depressed individuals demonstrating overt HPA axis abnormalities may range from 35% to 65%.

Maladaptive responses to stress and the associated GC hypersecretion can induce hyperemotional states, mood dysfunction, and cognitive impairments in depressed patients. This is often paralleled by volume changes in various brain regions, including the hippocampus. In the literature, variations in hippocampal volume have been reported in depression, which can relate to differences in disease duration, anatomical delineation, lateralization, early life conditions, and genotype. In general, amygdalar, prefrontal, and hippocampal changes in MDD are well-replicated findings in psychiatry (Cobb et al., 2013; Czéh, Fuchs, Wiborg, & Simon, 2015; Drevets, Price, & Furey, 2008; Kempton et al., 2011; Lorenzetti, Allen, Fornito, & Yücel, 2009). Whether hippocampal volume loss reflects a cause or a consequence of MDD remains unclear but lower hippocampal volumes in patients can be predicted by a more extensive depressive episode duration and recurrence, the size of their integrated cortisol responses, and a history of early life stress. Also, a smaller hippocampal volume could predispose for the development of psychopathology (Czéh & Lucassen, 2007; Lucassen et al., 2014; Sapolsky, 2000).

Preclinical and postmortem studies indicate that chronic stress and depression affect different hippocampal subfields, and different structural substrates, to a different extent. In addition to sex-specific changes in GR expression (Medina et al., 2013; Wang et al., 2012), differences across its transversal and longitudinal axis and connectivity changes were found. Detailed high-field MRI measurements (Huang et al., 2013) revealed that the mean volumes of the DG and CA1–3 subregions were smaller in non-medicated or recently unmedicated depressed patients than in healthy controls. Along the longitudinal axis, a smaller volume was mainly found posteriorly, i.e., in the hippocampal body and tail, rather than anteriorly. Of interest, both the subfield and the posterior hippocampal volume reductions seen in unmedicated depression were absent after antidepressant treatment. The posterior hippocampus may differ from the anterior part when studying volume changes or treatment outcome (Kheirbek & Hen, 2011; MacQueen, Yücel, Taylor, Macdonald, & Joffe, 2008).

In a postmortem study, total hippocampal volume in depression was decreased with increasing duration of depressive illness. There was no significant difference between depressed and control cases in the total number or density of neurons or glia in the CA1, CA2/3, hilus, or DG subregion (Cobb et al., 2013). However, both granule cell and glial cell numbers increased with age in depressed patients on medication, which may reflect proliferative effects of antidepressants (see below) and suggest that GC-induced volume reductions parallel to increased cellular densities are best explained by assuming cell shrinkage and changes in neuropil rather than cell loss (Lucassen et al., 2014; Stockmeier et al., 2004; Swaab et al., 2005). The finding that the loss of brain volume in Cushing's syndrome is reversible after correction of hypercortisolism is consistent with this concept (Bordeau et al., 2002; Starkman et al., 1999). Another option is that volume changes may relate to (lasting) changes in structural plasticity and/or neurogenesis (Czéh & Lucassen, 2007; Jacobs, van Praag, & Gage, 2000; Kempermann, Krebs, & Fabel, 2008; Sapolsky, 2000), as will be discussed below.

STRUCTURAL PLASTICITY AND ADULT NEUROGENESIS

Traditionally, MDD and stress-related disturbances were explained by neurochemical (mainly monoaminergic) imbalances, thought to take place mainly at the synaptic level. More recent studies have now indicated that impairments in structural plasticity also contribute to, e.g., the volumetric changes and pathophysiology of these disorders. Various candidate cellular substrates, such as dendritic retraction, spine alterations, neuronal loss, or glial changes, that are stress sensitive, have been proposed. However, it remains elusive whether changes in these substrates can be considered truly "pathological" or whether they reflect more dynamic adaptations to stress, that can, at least to some extent, be transient and/or reversible, as discussed before (Czéh & Lucassen, 2007; Heine, Maslam, Zareno, Joels, & Lucassen, 2004; Lucassen et al., 2014; Sapolsky, 2000).

One highly plastic and dynamic cellular substrate is adult neurogenesis (AN). AN refers to neural stem cells that continue to produce new neurons in the adult brain (see Fig. 8.1 for a schematic representation). New neuron formation in the adult hippocampus received considerable attention during recent years as it has been implicated, e.g., in (aspects of) mood, epilepsy, cognition, and pattern separation (Abrous & Wojtowicz, 2015; Aimone, Deng, Gage, 2011; Bielefeld et al., 2014; Cho et al., 2015; Clelland et al., 2009; Déry, Goldstein, & Becker, 2015; Jessberger et al., 2009; Jessberger & Gage, 2014; Oomen, Bekinschtein, Kent, Saksida, & Bussey, 2014; Oomen et al., 2013; Richetin et al., 2015; Sahay et al., 2011; Sierra et al., 2015; Tronel et al., 2015). Also, the adult-generated cells are regulated

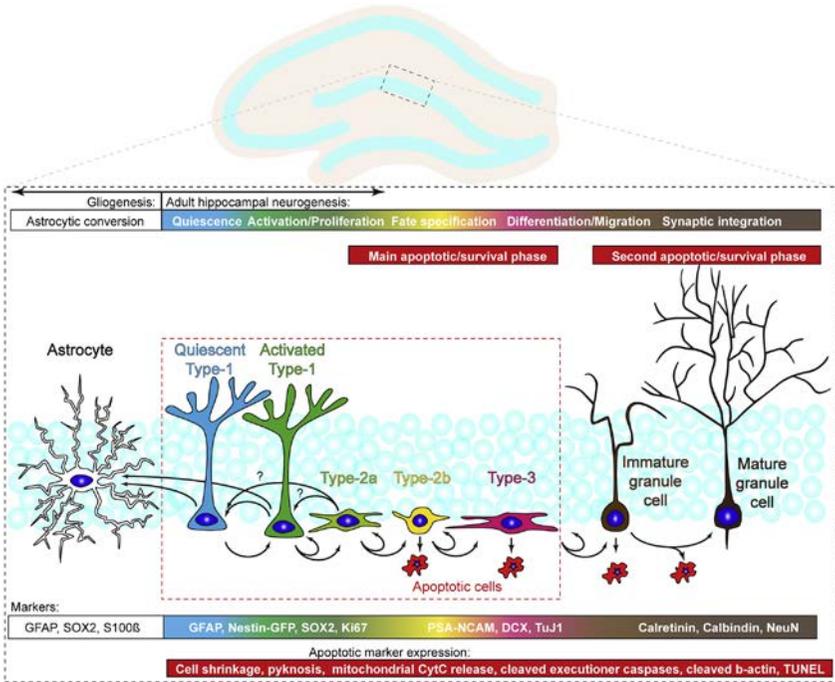


FIGURE 8.1 Schematic representation of neurogenesis in the adult hippocampus, showing the different stages of the neurogenic cascade, the different cell types, and the expression of some of the cell type-specific markers typically used to characterize them. *Arrows* indicate possible transitions between cell types originating from a type 1 neuronal stem cell (NSC) with self-renewal potential. The scheme is based on Encinas et al. (2006) and Sierra et al. (2010).

by (early) stress and various molecular factors. They express GRs (see Fig. 8.1 and Anacker et al., 2013; Gould, McEwen, Tanapat, Galea, & Fuchs, 1997; Heine, Maslam, Joëls, & Lucassen, 2004; Heine, Maslam, Zareno, et al., 2004; Lehmann, Brachman, Martinowich, Schloesser, & Herkenham, 2013; Lemaire, Koehl, Le Moal, & Abrous, 2000; Lucassen, Meerlo, et al., 2010; Lucassen, Fitzsimons, et al., 2013; Lucassen, Naninck, et al., 2013; Montaron et al., 2003; Pham, Nacher, Hof, & McEwen, 2003; Schoenfeld & Gould, 2013; Schouten, Buijink, Lucassen, & Fitzsimons, 2012; Schouten et al., 2015; Song et al., 2012; Wong & Herbert, 2004, 2005) and have been implicated in cognition, anxiety, pattern separation, behavioral flexibility, and the pathophysiology of depression (Clelland et al., 2009; Déry et al., 2015; Duman, 2004; Eisch & Petrik, 2012; Fitzsimons et al., 2013; Jacobs et al., 2000; Kempermann, 2008; Kempermann et al., 2008; Kempermann & Kronenberg, 2003; Lucassen, Meerlo, et al., 2010; Lucassen et al., 2014; Lucassen, Stumpel, Wang, Aronica, 2010; Opendak & Gould, 2015; Petrik, Lagace, & Eisch, 2012; Revest et al., 2009).

The neurogenic hypothesis of depression was postulated based on three observations. First, stress is a risk factor for the development of depression and associated with reductions in hippocampal volume. Stress also reduces neurogenesis in the hippocampus. Second, most antidepressants generally require a period of several weeks to exert their beneficial action, similar to the time frame that newborn neuronal precursors need to integrate and contribute as functional neurons to the adult DG circuitry. Third, antidepressant treatment and the resulting increases in serotonin levels, e.g., promote cell proliferation and generation of new neurons in the hippocampus (Boldrini et al., 2012; Malberg & Duman, 2003; Sahay & Hen, 2007; Wu et al., 2014) that has further been implicated in stress response regulation (Anacker & Pariante, 2012; Lucassen, Fitzsimons, et al., 2013; Opendak & Gould, 2011; Snyder, Soumier, Brewer, Pickel, & Cameron, 2011; Surget et al., 2011).

It is important to note that exceptions exist too, where neurogenesis or newborn cell survival is not stimulated by antidepressants, an effect that appears to depend on animal species and mouse strain, sex, age, and early life history, and on the pharmacology of the antidepressant, or may become apparent only under disease-specific conditions, or only in more anxious mouse strains (Couillard-Despres et al., 2009; Cowen, Takase, Fornal, Jacobs, 2008; David et al., 2009; Hodes, Hill-Smith, Suckow, Cooper, Lucki, 2009; Hodes, Yang, Van Kooy, Santollo, & Shors, 2009; Holick, Lee, Hen, & Dulawa, 2008; Huang, Bannerman, Flint, 2008; Klomp, Václavů, Meerhoff, Reneman, & Lucassen, 2014; Marlatt, Lucassen, & van Praag, 2010; Mendez-David et al., 2014; Navailles, Hof, & Schmauss, 2008; Santarelli et al., 2003; Snyder et al., 2009). Also, anatomical differences within the hippocampus are involved (Kheirbek & Hen, 2011) while indirect effects of serotonin, e.g., on other forms of plasticity, or in interaction with other drugs, may also influence antidepressant effects on neurogenesis and brain plasticity (Maya Vetencourt et al., 2008; Wu & Castrén, 2009). Moreover, a reduction in neurogenesis per se, i.e., other than induced by stress, does not cause a “depressed” phenotype (Henn & Vollmayr, 2004; Lucassen, Fitzsimons, et al., 2013; Snyder et al., 2011; Vollmayr, Simonis, Weber, Gass, & Henn, 2003). Later studies have suggested that neurogenesis is implicated in antidepressant drug actions in rodents and primates and that blocking the proneurogenic effects of antidepressants prevented the behavioral effects of these drugs measured in some animal models (see also Figs. 8.1 and 8.2, and Santarelli et al., 2003; Sahay & Hen, 2007; Surget et al., 2008; Perera et al., 2011).

So far, however, a coherent functional theory is still lacking as to how a limited number of new hippocampal neurons in only a subregion of the DG can contribute to brain features and functions that are as general as mood or depressive symptoms. This is besides the cognitive deficits, which are related to, but not specific for, mood disorders. Although a reduced rate

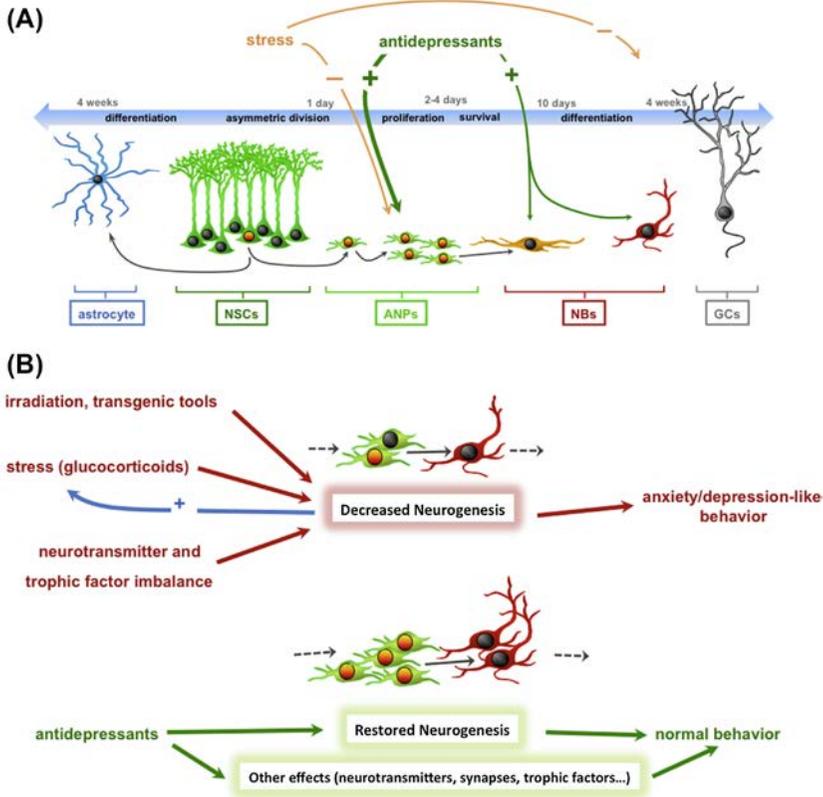


FIGURE 8.2 Schematic representation of the different stages of neurogenesis and their relationship/sensitivity to stress and depression. (A) Model of adult hippocampal neurogenesis. Neural stem cells (NSCs) are activated and enter the cell cycle to produce amplifying neuronal precursors (ANPs). These can proliferate and die, or differentiate into neuroblasts (NBs) and eventually into granule cells (GCs). Stress can reduce newborn cell proliferation and also their survival and differentiation (see also Heine, Maslam, Joëls, et al., 2004; Heine, Maslam, Zareno, et al., 2004 and Wong and Herbert, 2004). Many antidepressants, including treatment with antiglucocorticoids, exert the opposite effect. (B) An acute decrease in neurogenesis per se is not sufficient to provoke depression or depression-like behavior, but when neurogenesis is decreased by an imbalance of neurotransmitters or trophic factors, or induced with transgenic tools or, e.g., irradiation, it can increase the response to stress, which by itself can further diminish neurogenesis (blue +). As a result, depression-like behavior can emerge in experimental animals. Most antidepressants increase neurogenesis, a response that has been shown to be required for their (functional) antidepressant action, most likely in combination with other effects at the neurotransmitter, trophic factor, and/or synaptic levels. Chronic exposure to stress, or to stress early in life, can lastingly reduce AN, resulting in a diminished neurogenic reserve and a reduced cognitive potential and flexibility, associated with depression (Kheirbek, Klemenhagen, Sahay, & Hen, 2012).

of neurogenesis may reflect impaired hippocampal plasticity, reductions in adult neurogenesis alone are unlikely to produce depression. Lasting reductions in the turnover rate of DG granule cells, however, will, over time, clearly alter the average age and overall composition of the DG cell population and thereby influence properties of the hippocampal circuit.

Neural stem cells present in the hippocampus and their progeny go through different stages of proliferation (apoptotic), cell selection, fate specification, migration, and neuronal differentiation before they are eventually integrated as new functional neurons into the preexisting adult hippocampal network (Fig. 8.1) (Abrous et al., 2005; Jessberger & Gage, 2014; Kempermann, 2012; Opendak & Gould, 2015; Zhao, Deng, & Gage, 2008). Neurogenesis and related structural plasticity have also been reported in other brain structures, such as the amygdala, striatum, hypothalamus, and neocortex, but to a more limited extent, with differences between species and often occurring in response to specific challenges or injury. Whether the cellular/structural plasticity in these other brain regions is also regulated by similar environmental factors, such as stress, is less well studied (Amrein, Isler, & Lipp, 2011; Cavegn et al., 2013; Gould, 2007).

AN is dynamically regulated by various hormonal and environmental factors and drugs and declines with age. Neurogenesis in the hippocampal DG is potently stimulated by exercise and environmental enrichment, notably parallel to changes in hippocampal function (Holmes, Galea, Mistlberger, & Kempermann, 2004; Kannangara et al., 2011; Kempermann, 2012; Kempermann et al., 2010; Kobilov et al., 2011; Vivar, Potter, & van Praag, 2013; Voss et al., 2013). Exercise also exerts effects on the stress axis itself (Droste et al., 2003) and on growth factor levels (Marlatt, Potter, Lucassen, & van Praag, 2012; Vivar et al., 2013). Whereas rewarding experiences can also stimulate neurogenesis, aversive experiences like stress generally decrease proliferation and neurogenesis in the hippocampus (Balu & Lucki, 2009; Lucassen, Meerlo, et al., 2010; Lucassen et al., 2014).

STRESS REGULATION OF NEUROGENESIS

Stress is one of the best known environmental inhibitors of AN. Both psychosocial (Czeh et al., 2002; Gould et al., 1997) and physical stressors (Malberg & Duman, 2003; Pham et al., 2003; Vollmayr et al., 2003) can suppress one or more phases of the neurogenesis process (see Figs. 8.2 and 8.3 and Czeh et al., 2001, 2006, 2002; Lucassen, Meerlo, et al., 2010; Lucassen et al., 2014; Mirescu & Gould, 2006). In classical studies, predator stress produced significant reductions in hippocampal proliferation (Czeh et al., 2001; Gould et al., 1997; see Lucassen et al., 2014, and Czeh et al., 2015, for recent reviews) and both acute and chronic unpredictable stress can suppress proliferation while also other stressors, including physical restraint,

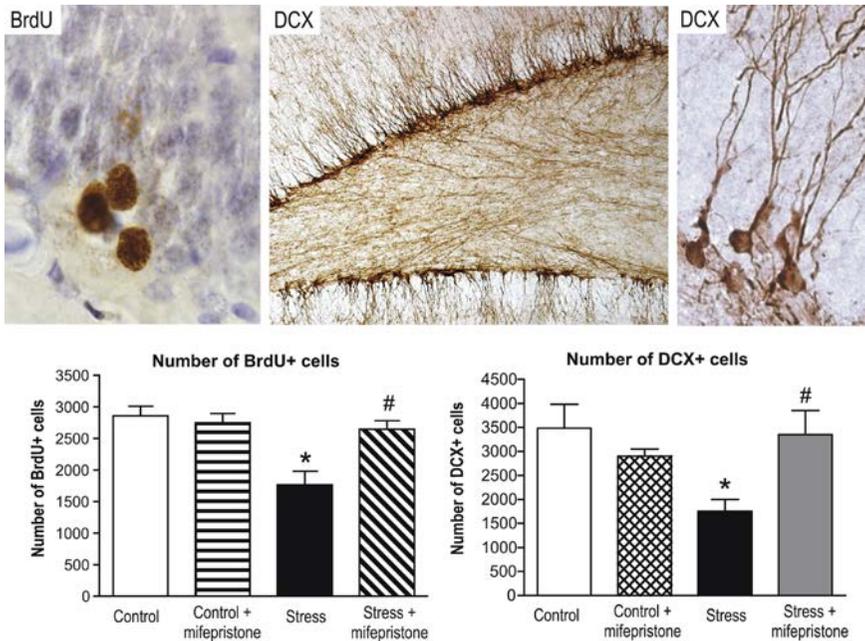


FIGURE 8.3 Effects of prolonged stress or glucocorticoid treatment on neurogenesis and the rescue effect of GR blockade. Top panels show examples of BrdU+ and Doublecortin (DCX)+ immunostained cells in the rat hippocampal dentate gyrus (DG). DCX-positive somata are located in the SGZ with their extensions (arrowheads) passing through the GCL. Lower panels display BrdU- (left graph) and DCX-positive cell numbers (right graph) in a 1 in 10 series of hippocampal sections of rats subjected to 21 days of chronic unpredictable stress (Oomen et al., 2007) similar results have been found after chronic corticosterone treatment (Mayer et al., 2006). The significant reduction in both BrdU- (21-day-old cells) and DCX-positive cell numbers after chronic stress or corticosterone treatment is normalized by 4 days of high dose treatment with the GR antagonist mifepristone, whereas the drug alone has no effect (see Mayer et al., 2006, and Oomen et al., 2007; Zalachoras et al., 2013, for details). * indicates $p < 0.001$ relative to the control group in the left graph and $p < 0.05$ in the right graph. Similar recovery is found when mifepristone is applied for only 1 day (Hu et al., 2012).

social defeat, inescapable foot shock, sleep deprivation, and inflammation can decrease the numbers of new neurons in the dentate gyrus (Czéh et al., 2002; Dagyte et al., 2009; Gould et al., 1997; Heine, Maslam, Joëls, et al., 2004; Heine, Maslam, Zareno, et al., 2004; Hulshof, Novati, Luiten, den Boer, & Meerlo, 2012; Lucassen, Meerlo, et al., 2010; Lucassen, Stumpel, et al., 2010; Pham et al., 2003; Schoenfeld & Gould, 2013; Wu et al., 2014). Interestingly, also an absence of an effect or even increases in neurogenesis have been reported after stress in some instances, but here, differences in temporal design may have been involved, or repeated stressors could have become predictable or were relatively mild and may actually have enriched an otherwise “boring” environment and could thus have been perceived as rewarding experiences (Parihar, Hattiangady, Kuruba, Shuai, & Shetty, 2011).

Also the duration of the stress period and the anatomical location may be of influence as acute stress could, e.g., induce proliferation in the dorsal hippocampus under specific conditions (Kirby et al., 2013; Kheirbek & Hen, 2011).

When no other transmitter systems are altered, the stressor is unpredictable and its nature severe, then reductions in neurogenesis are commonly seen. In fact, multiple stages of the neurogenic process are then affected, including proliferation of the neural stem cells and amplifying progenitor cells, as well as subsequent neuronal differentiation phase and dendritic expansion. Stress not only reduces proliferation and neurogenesis in many different species, it may also shift neural stem cells away from neuronal differentiation and instead “redirect” them toward the generation of oligodendrocytes (Chetty et al., 2014). Although not studied in great detail yet, such stress-induced fate shifts may have important functional consequences, e.g., for the myelination of axons and/or mossy fibers, and hence network connectivity.

Thus, while different types of stress can trigger different behavioral and functional responses, GCs are considered instrumental in mediating the effects of stress, e.g., on new neuron production. Chronic exogenous administration of GCs to animals affects cell proliferation, neuronal differentiation, and cell survival, as well as the production of oligodendrocytes and (micro-)glia responses and behavior (Bland et al., 2010; Butovsky et al., 2006; Chetty et al., 2014; Ekdahl, Kokaia, & Lindvall, 2009; Hu et al., 2012; Lehmann et al., 2013; Mayer et al., 2006). Moreover, the reductions in neurogenesis after stress, and many of the related molecular alterations as well (Datson et al., 2012), can be prevented by, e.g., blocking GCs from the adrenal or HPA mediators, using, e.g., CRH or GR antagonists (Alonso et al., 2004). Also, a short treatment for 1 or 3 days with a GR antagonist already normalized stress or GC-induced reductions in hippocampal neurogenesis (Hu et al., 2012; Mayer et al., 2006; Oomen, Mayer, de Kloet, Joels, & Lucassen, 2007; Zalachoras et al., 2013) (see also Fig. 8.3).

Although more information has become available on molecular control and timing of stem cell regulation (Anacker et al., 2013; Fitzsimons et al., 2014, 2013; Miller et al., 2013; Schouten et al., 2012, 2015), the precise mechanisms by which GCs decrease neurogenesis remains unknown. NMDA receptors, GRs, and MRs are present on the new cells, albeit in different ratios over time, that likely act in concert to mediate effects of stress on neurogenesis (Montaron et al., 2003; Wong & Herbert, 2004, 2005). Notably, GR knockdown, selectively in cells of the hippocampal neurogenic niche, accelerates their neuronal differentiation and migration, induces ectopic positioning, alters their dendritic complexity, and increases their dendritic spines and basal excitability but impairs contextual freezing during fear conditioning (Fitzsimons et al., 2013). Hence, GR expression in, and thus stress sensitivity of, the newborn hippocampal cells is important for their structural and functional integration in the hippocampal circuit.

The precursors are further located closely to blood vessels, which is of relevance as it is indeed this population that is particularly sensitive to stress (Heine, Zareno, Maslam, Joels, & Lucassen, 2005). Astrocytes are also important as this cell type supports the survival of developing neurons, possesses GR, and are affected by some types of stress (Banar & Duman, 2008; Czéh, Simon, Schmelting, Hiemke, & Fuchs, 2006; Oomen et al., 2009) and changes in this cell population can contribute to depressive-like behavior (Banar & Duman, 2008).

Stress further slows down neuronal differentiation, as evidenced by the upregulation of markers indicating cell cycle arrest (Heine, Maslam, Joels, et al., 2004) and related changes in granule cell dendritic trees. Stress and GCs also reduce the survival of neurons produced prior to the stressful experience. While the underlying mechanism is largely unknown, this is thought to be mediated by inhibitory effects on neurotrophins such as brain-derived neurotrophic factor (BDNF) (Schmidt & Duman, 2007). The reduction in newborn cell survival likely also involves microglia, which are known to phagocytose newborn neuronal precursors (Ekdahl et al., 2009; Guadagno et al., 2013; Hinwood, Morandini, Day, & Walker, 2012; Morris, Clark, Zinn, & Vissel, 2013; Sierra et al., 2010). Indeed, stress influences microglia and their responsivity, which may modulate their efficiency in cleaning up debris. Although under normal conditions, “resting” or unchallenged microglia do not trigger apoptosis of those cells that they efficiently phagocytose in the hippocampal neurogenic niche (Sierra et al., 2010), microglia could help reduce new neuron survival under acute and chronic stress (Jakubs et al., 2008), by becoming activated and releasing cytokines and chemokines with neurotoxic effects (Johansson, Price, & Modo, 2008; Koo & Duman, 2008; Spulber, Oprica, Bartfai, Winblad, & Schultzberg, 2008). Also, they could undergo changes in intrinsic properties such as motility and morphology (Walker, Nilsson, & Jones, 2013). Whether they have the capacity to switch to a model in which they can actually induce apoptosis of neuronal precursors in the hippocampal neurogenic niche, as has been shown in vitro via TNF α (Guadagno et al., 2013), remains to be determined.

Although a role for (nor)adrenaline has not been studied in detail with respect to stress-induced changes in neurogenesis, an important difference between several studies is whether or not GC levels remain elevated after the exposure to the stressor has ended. In some psychosocial stress models, the GC “milieu” is altered in a lasting manner and GC levels remain elevated for prolonged periods of time, which has stronger inhibitory effects on AN than apparently severe, but predictable, physical stressors, such as restraint (Wong & Herbert, 2004). Several examples of a persistent and lasting inhibition of AN after an initial stressor exist, despite a later normalization of GC levels (e.g., Czéh et al., 2002; Mirescu & Gould, 2006; Schoenfeld & Gould, 2013). Also, GC levels can remain elevated after the onset of the first, often psychosocial, stressor that suppresses neurogenesis

for prolonged periods. In other, milder models, stress hormone levels generally normalize, yet neurogenesis remains reduced (Schoenfeld & Gould, 2013; Van Bokhoven et al., 2011). This suggests that while GCs are involved in the initial suppression of proliferation, they are not always necessary for the maintenance of this effect.

When studying the effects of stress on adult neurogenesis under laboratory conditions, it is important to realize that many variables influence the outcome of such studies, as interindividual and gender differences in stress coping, handling, time of day at sacrifice, and previous exposure to stressful learning tasks can influence stress responses and neurogenesis (e.g., Ehninger & Kempermann, 2006; Holmes et al., 2004). In addition to stress hormones like GCs, also other mediators of the stress system that interact with neurogenesis are changed. Models employing repeated injections with exogenous GCs to imitate the hypercortisolism found, e.g., in depression, exert negative feedback at the level of the pituitary and inhibit the endogenous production of GCs by the adrenals. As a result, ACTH and CRH levels are very low in GC-treated rodents, a condition which is in contrast to the endogenous HPA axis activation seen in chronically stressed animals and patients where CRH, ACTH, and GCs are elevated. A large number of other factors may also contribute to the stress-induced inhibition of AN, such as the stress-induced increase in glutamate release via NMDA receptor activation (Gould et al., 1997; Nacher & McEwen, 2006; Schoenfeld & Gould, 2013).

Stress further affects various neurotransmitters implicated in the regulation of neurogenesis: GABA (Ge, Yang, Hsu, Ming, & Song, 2007), serotonin (Djavadian, 2004), noradrenaline (Joca et al., 2007), acetylcholine (Bruel-Jungerman, Lucassen, & Francis, 2011), and dopamine, e.g., (Domínguez-Escribà et al., 2006; Takamura et al., 2014). GABA deserves special mention as it has been recently reported to be a key regulator for the recruitment and activation of hippocampal neural stem cells. The balance of activation and quiescence would be controlled by tonic release of GABA by neighboring interneurons. Higher levels would promote quiescence while lower levels would promote activation of neural stem cells, via GABAA receptors expressed by them (Song et al., 2012). Also other neurotransmitter systems such as the cannabinoids, opioids, nitric oxide, various neuropeptides, and also gonadal steroids may contribute (see, e.g., Balu & Lucki, 2009; Galea, 2008). Importantly, stress reduces the expression of several growth and neurotrophic factors, such as BDNF, insulin-like growth factor-1, nerve growth factor, epidermal growth factor, and vascular endothelial growth factor, that can influence neurogenesis (see, e.g., Schmidt & Duman, 2007; Wilson, 2014).

Chronic stress can also affect proliferation of glial cells as, e.g., seen in the medial prefrontal cortex of rats after social defeat, after chronic unpredictable stress, or after chronic GC administration. Similarly, prolonged

and elevated GC treatment inhibited NG2-positive cell proliferation, reflecting changes in oligodendrocyte precursors. Chronic stress also promotes structural remodeling of microglia and can enhance the release of proinflammatory cytokines from microglia, and can even mediate aspects of depressive-like behavior (Kreisel et al., 2014).

Astrocytes are also key components of the “neurogenic niche” that provides the necessary local microenvironment for neurogenesis. For instance, astrocytes participate physically in the establishment of synapses between newborn and preexistent neurons, and the inhibition of glutamate reuptake by astrocytes significantly impairs postsynaptic currents and facilitates paired-pulse facilitation in adult-born neurons (Krzisch et al., 2015). Furthermore, astrocytes promote neuronal differentiation by secreting ephrin-B2 acting on ephrin-B4 receptors present in neural stem cells and modulating β -catenin in a Wnt-independent manner (Ashton et al., 2012). Since astrocytes also contain GRs and can be regulated by stress, this implies that stress can also modulate neural progenitors through interactions with astrocytes (Vallieres et al., 2002; Wang et al., 2013).

Stress-induced suppression of adult neurogenesis has been associated with impaired performance on various cognitive tasks that require the hippocampus, such as spatial navigation learning and object memory (Braun & Jessberger, 2014; Oomen et al., 2014). It should be noted that these effects are typically observed within a shorter time frame than what would be expected for the involvement and integration of newborn neurons, which should be taken into account in the experimental design. In addition, additional younger, immature, and excitable neurons, as well as the older populations of DG cells, exist that are sensitive too, and could contribute to hippocampal performance. As a more specific test for the new neurons in the DG per se, pattern separation has received a lot of attention recently (see above).

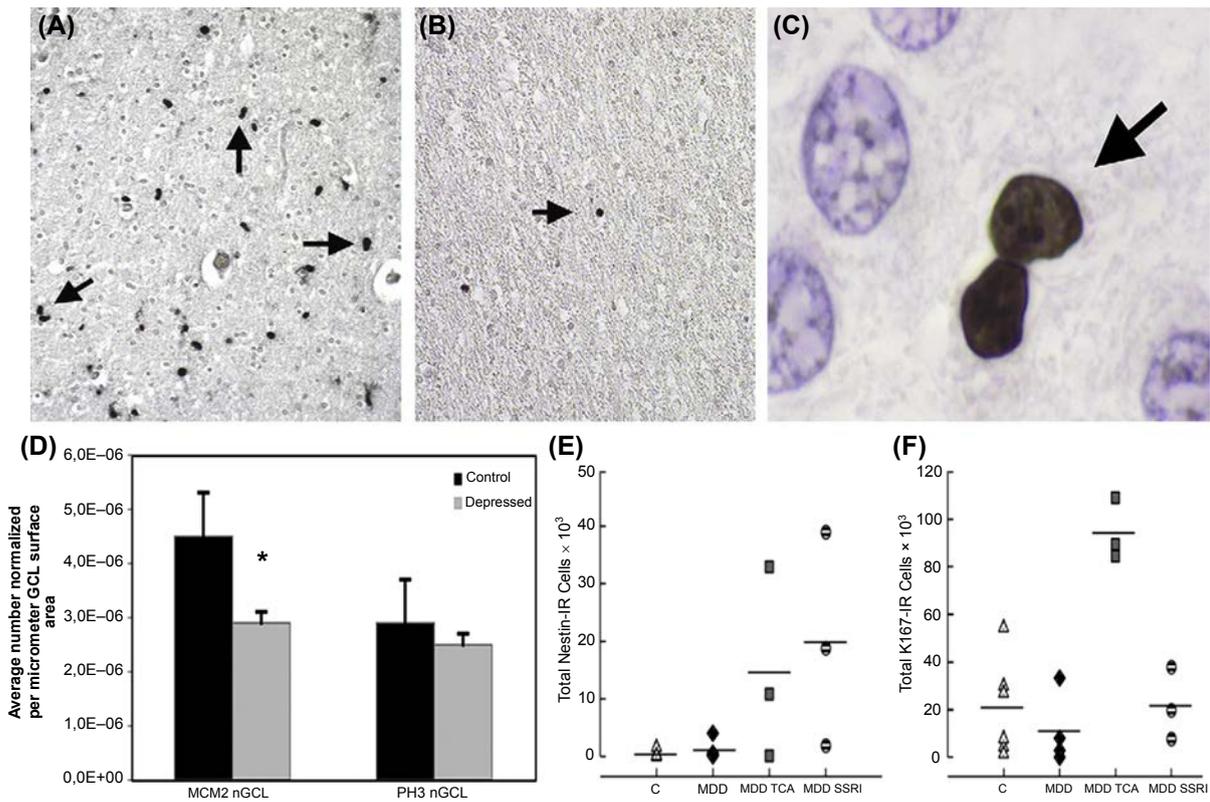
An extensive literature further indicates that AN is sensitive to stress exposure during the early life period. As this is beyond the scope of this chapter, early life stress will only be discussed briefly. The set point of HPA axis activity, and possibly also of neurogenesis regulation, is, on the one hand, programmed by genotype, but can be further modified by early development, and, e.g., by epigenetic changes (Lucassen, Naninck, et al., 2013). In humans, early life stressors (ELS) are among the strongest predisposing factors for developing psychopathology and cognitive decline later in life (Baram et al., 2012; Heim et al., 2008; Loman, Gunnar, & Early Experience Stress and Neurobehavioral Development Center, 2010; Maselko, Kubzansky, Lipsitt, & Buka, 2011; Risch et al., 2009; Teicher, Anderson, & Polcari, 2012) and in experimental conditions where emotional and cognitive functions are altered after ELS (Aisa, Tordera, Lasheras, Del Río, & Ramírez, 2007; Baram et al., 2012; Brunson et al., 2005; Ivy et al., 2010; Oomen et al., 2010). Also neurogenesis is sensitive to stress during the perinatal period, the effects of which often depend on sex and

on the developmental stage during which the organism experienced stress (Coe et al., 2003; Galea, 2008; Kim et al., 2013; Korosi et al., 2012; Lemaire et al., 2000; Loi, Koricka, Lucassen, & Joëls, 2014; Lucassen et al., 2009; Lucassen, Naninck, et al., 2013; Mirescu et al., 2004; Naninck et al., 2015), although exceptions exist as well (Tauber et al., 2008).

NEUROGENESIS AND MAJOR DEPRESSION

Given the clear association among stress, hippocampal volume reductions, and major depression, it came as no surprise that antidepressants could affect hippocampal neurogenesis in several animal models (for a recent overview, see Czéh et al., 2015). Given the technical limitations to visualize neurogenesis in vivo, only few studies have so far addressed this issue in human brain tissue. Reif, Fritzen, Finger, Strobel, and Lauer (2006) failed to find differences in neural stem cell proliferation in postmortem brain samples between patients suffering from MDD, bipolar disorder, or schizophrenia and control subjects. Antidepressants did not alter these numbers but changes were found in schizophrenia. More recent studies (Boldrini et al., 2012, 2009; Lucassen et al., 2014; Lucassen, Stumpel, et al., 2010) (see Fig. 8.4) compared progenitor and dividing cells with different immunocytochemical markers and found that in hippocampal tissues of untreated depressed subjects, the numbers of progenitor cells were significantly decreased. Both treatments with selective serotonin-reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) increased the number of nestin-positive progenitors and TCAs had a robust stimulatory effect on the number of Ki-67-reactive dividing cells. These changes were reported in middle aged (Boldrini et al., 2012, 2009) but not in older depressed patients (Lucassen, Meerlo, et al., 2010; Lucassen, Stumpel, et al., 2010), possibly because of limited power or due to age-related differences in plasticity in these patients (see also Felice et al., 2015).

In a postmortem study on MDD patients, the volume of the histologically defined DG was determined and found to be in fact 68% larger in SSRI-treated depressed subjects, while SSRI treatment substantially increased neural progenitor cells in the dentate gyrus. A recent study by Huang et al. (2013) found smaller DG volumes using MRI in unmedicated depressed patients, which was confirmed at postmortem analysis, which is consistent with the neurogenic hypothesis of depression. Interestingly, both subfield and posterior hippocampal volume reductions were only seen in unmedicated depression but were absent in patients treated with antidepressants. Although it is so far not simple to detect ongoing neurogenesis in vivo (Manganas et al., 2007), these data are consistent with pre-clinical studies demonstrating subregional specific and opposite effects of stress or depression and antidepressant treatment.



Although AN may thus not be essential for the development of depression, it may be required for clinically effective antidepressant treatment (Perera et al., 2011; Santarelli et al., 2003; Surget et al., 2008, 2011). Hence, stimulation of neurogenesis has been regarded as a promising strategy for identifying new antidepressant targets (see also Figs. 8.1 and 8.2). Accordingly, when tested in chronic stress paradigms, several candidate antidepressant compounds, such as corticotrophin-releasing factor (CRF1), vasopressin (V1b), or glucocorticoid receptor antagonists (Alonso et al., 2004; Oomen et al., 2007; Surget et al., 2008), tianeptine (Czéh et al., 2001) or selective neurokinin-1 (NK1) receptor antagonists (Czéh et al., 2005) could indeed normalize the inhibitory effects of stress on proliferation or neurogenesis.

Hippocampal volume loss is well documented in various psychopathologies and also in patients with Cushing's disease and in subjects treated with synthetic GCs (Bourdeau et al., 2002; for a review, see Lucassen et al., 2014, and references therein). In addition to neurochemical changes, structural connectivity and plasticity changes, including neurogenesis, may contribute to its etiology as well. However, it remains elusive how exactly a subpopulation of newborn neurons can contribute to general features such as stress regulation, mood, and depression (Anacker & Pariante, 2012; Lehmann et al., 2013; Lucassen, Fitzsimons, et al., 2013; Lucassen et al., 2014; Opendak & Gould, 2011; Snyder et al., 2011).

Although a reduced rate of neurogenesis may reflect impaired hippocampal plasticity, reductions in adult neurogenesis per se, i.e., induced by irradiation, but without the concomitant presence of stress, are unlikely to

FIGURE 8.4 Changes in cell proliferation in postmortem human brain tissue of depressed and antidepressant-treated patients. (A) Cells immunopositive for the cell cycle marker minichromosome maintenance protein 2 (MCM2) that is involved in the control of DNA replication. Many MCM2-immunopositive cells and doublets (arrows) are observed in cortical tissue of a 2-year-old subject that served as positive control for the immunocytochemical procedure. (B) As expected, MCM2-ir cell numbers are strongly reduced to very low numbers (arrow) in a 69-year-old control subject. (C) Detail of an MCM2-ir doublet of two cells that appear to have recently separated in the hippocampus of a depressed patient (arrow), cresyl violet counterstain. (D) Graphs depicting numbers of MCM2 and phosphorylated histone H3 (PH3)-immunopositive cells (the latter marker reflecting the late G2 and M phases of cell division). PH3-immunoreactive cells in the subgranular zone and granular cell layer of the dentate gyrus, normalized to the surface area of the GCL. A significant reduction was found for MCM2, but not PH3, in elderly (average age of 68 years) depressed patients compared to controls. (E) Neural progenitor and (F) dividing cells (nestin and Ki-67-positive, respectively) are increased in the dentate gyrus of younger (average ages of 40 and 54 years) patients with major depressive disorder (MDD) who were treated with antidepressants compared to untreated MDDs and control subjects. Progenitor numbers (E, nestin-positive) were higher in MDD patients treated with tricyclics (TCA) or with selective serotonin reuptake inhibitors (SSRI), compared to untreated MDD and control cases, whereas the numbers of dividing cells (F, Ki-67-ir) were higher only in the TCA but not the SSRI-treated group. *Reproduced from Lucassen P.J., Pruessner J., Sousa N., Almeida O.F., Van Dam A.M., Rajkowska G., et al. (2014). Neuropathology of stress. Acta Neuropathologica, 127, 109–135.*

produce depression (Henn & Vollmayr, 2004). Lasting and stress-related reductions in DG neurogenesis will, however, alter turnover rate, average cellular age, and overall composition of the DG, and in the long term modify DG volume, and thereby influence the properties and vulnerability of the hippocampal circuit (Teicher et al., 2012). Indeed, hippocampal volume changes often coincide with stressful episodes in depressed patients, correlating with cognitive impairments.

The hippocampus is further thought to provide negative feedback control of the HPA axis, in which neurogenesis is at least partly implicated. Initial disturbances in hippocampal neurogenesis or output may thus disturb feedback and hence amplify HPA axis dysregulation that is common in approximately 50% of the depressed patients. Since massive cell loss could not be demonstrated in the hippocampus, the observed hippocampal volume changes could be due to (atrophy of) the somatodendritic or synaptic components, but also glia or changes in fluid balance may be involved (Czéh et al., 2006; Lucassen et al., 2014). Interestingly, AN might form a link between depression and stress. When neurogenesis is ablated, either by X-irradiation or by selective killing of mitotically active GFAP-expressing cells (neural stem cells) in mice, stressors induce a significantly stronger effect, measured both by blood levels of cortisone and by behavioral outcome in tests such as novelty-suppressed feeding, forced swimming, and the sucrose preference test (Snyder et al., 2011). Thus AN has been postulated to act as a buffer to both stress responses and depressive behavior.

CONCLUSIONS

Different types of stress and glucocorticoid and antidepressant treatment often interfere with one or more phases of the neurogenetic process. While inhibitory effects of acute stress can normalize after a recovery period, e.g., reductions in neurogenesis that are caused by chronic, severe, and/or unpredictable stress may last longer and have functional consequences. While neurogenesis has been implicated in cognition, mood, and anxiety regulation as well as in the therapeutic effects of antidepressant drugs, its exact role, i.e., cause or consequence, in relation to depression remains poorly understood. A reduced rate of neurogenesis may reflect impaired hippocampal plasticity, but reductions in AN alone are unlikely to produce depression and may require additional stress exposure, e.g., during critical developmental periods. Lasting reductions in turnover rate of DG granule cells, e.g., influenced by genotype or programmed by early life events, may alter the overall composition of the DG cell population. This, in turn, could modify stress responsivity and thereby influence functioning of the adult hippocampal circuit as well as the vulnerability for developing brain disorders.

Acknowledgments

P.J.L. is supported by grants from the HersenStichting Nederland, NWO PrioMedChild, and Amsterdam Brain and Cognition (ABC). C.P.F. and M.S. are supported by ISAO and by the Innovational Research Incentive Scheme VIDI from The Netherlands Organization for Scientific Research (NWO). J.M.E. is supported by MINECO (Spanish Ministry for Economy and Competitiveness) and IKERBASQUE (The Basque Science Foundation).

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