Differential Effects of Stress and Glucocorticoids on Adult Neurogenesis

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Abstract Stress is known to inhibit neuronal growth in the hippocampus. In addition to reducing the size and complexity of the dendritic tree, stress and elevated glucocorticoid levels are known to inhibit adult neurogenesis. Despite the negative effects of stress hormones on progenitor cell proliferation in the hippocampus, some experiences which produce robust increases in glucocorticoid levels actually promote neuronal growth. These experiences, including running, mating, enriched environment living, and intracranial self-stimulation, all share in common a strong hedonic component. Taken together, the findings suggest that rewarding experiences buffer progenitor cells in the dentate gyrus from the negative effects of elevated stress hormones. This chapter considers the evidence that stress and glucocorticoids inhibit neuronal growth along with the paradoxical findings of enhanced neuronal growth under rewarding conditions with a view toward understanding the underlying biological mechanisms.

Keywords Stress · Neurogenesis · Dentate gyrus · Reward · Learning · Anxiety · Physical activity · Sexual experience

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1 Introduction

"Stress" has been classically defined as an environmental challenge that produces a physiological response resulting in the release of specific "stress" hormones such as glucocorticoids (McEwen 2002; Sapolsky 2004). Although this classic definition seems neutral, another implicit aspect of most definitions of "stress" is that the environmental challenge has an aversive component. Although neutral or even appetitive stimuli can activate stress hormone systems, the most common contemporary definition of stress connotes a negative state.

It is now generally accepted that stress has detrimental actions on the structure and function of the hippocampus (reviewed in Conrad 2010). Stress is known to alter hippocampal structure and synaptic plasticity in a variety of ways, including decreasing dendritic arborization and spine density (Watanabe et al. 1992; Magariños et al. 1996; McKittrick et al. 2000; Bessa et al. 2009; Christian et al. 2011), decreasing cell proliferation and adult neurogenesis (Gould et al. 1997; Pham et al. 2003; Ferragud et al. 2010), reducing overall hippocampal volume (Golub et al. 2011; Pham et al. 2003), and reducing hippocampal LTP (Foy et al. 1987; Shors et al. 1997; Pavlides et al. 2002), although this latter effect seems to be specific to dorsal subsections of the hippocampus (Maggio and Segal 2007). All of these alterations have been proposed as mediators of stress-induced impairments in hippocampal-dependent learning (Conrad 2006; Howland and Wang 2008; Leuner and Gould 2010). However, more recent work demonstrating either no effects or even positive effects of elevated stress hormones on hippocampal structure and function suggests a broader view is necessary. This review will focus on both negative and positive effects of stress on adult neurogenesis, various modulators of these effects, and functional relevance of changes in hippocampal structure, with an emphasis on adult neurogenesis.

1.1 Adult Neurogenesis in the Mammalian Brain

Because the production of new neurons leads to synaptogenesis, as well as axonal elongation and dendritic elaboration, adult neurogenesis is perhaps the most fundamental of all types of structural change. The rate of adult neurogenesis in the mammalian brain is highest in two regions; the subgranular zone (SGZ), of the dentate gyrus, and subventricular zone (SVZ), from which new neurons migrate to the olfactory bulb (see Sects. 2.1 and 2.2 of this edition). Adult neurogenesis can be divided into three distinct stages: cell proliferation, neuronal differentiation, and cell survival (Christie and Cameron 2006). Each stage represents a plastic process that can be influenced by stress.

Cell proliferation refers to the mitosis of progenitor cells located in the SGZ of the dentate gyrus and the SVZ. Neuronal differentiation refers to the development of daughter cells into neurons. Most new cells in the dentate gyrus differentiate into granule neurons (80–95 %, depending on factors such as species, age, and location of granule cells within the dentate gyrus (Cameron et al. 1993b; Cameron and McKay 2001; Brown et al. 2003; Snyder et al. 2009a). A smaller percentage of new cells ($\sim$10), become glia (Cameron et al. 1993b; Steiner et al. 2004). In the SVZ, new cells migrate along the rostral migratory stream (Luskin 1993; Lois and Alvarez-Buylla 1994) where $\sim$95 % differentiate into granule cells (Lledo and Saghatelyan 2005) with the rest becoming periglomerular cells. The time course of maturation of new cells into neurons in the dentate gyrus can vary, as research has shown that new cells in the adult rat dentate gyrus select a neuronal fate more quickly than those in the adult mouse (Snyder et al. 2009a).

New neurons undergo morphological and electrophysiological alterations as they mature. By a few weeks after cell proliferation, new neurons develop the morphological characteristics of granule cells. New granule cells in the dentate gyrus grow dendritic arbors extending toward the molecular layer (Ribak et al. 2004), send axons into the CA3 region of the hippocampus (Hastings and Gould 1999; Zhao et al. 2006), generate action potentials (van Praag et al. 2002), and are activated by functionally relevant cues (Ramirez-Amaya et al. 2006; Tashiro et al. 2007; Snyder et al. 2012). In the olfactory bulb, new granule cells exhibit dynamic dendritic growth and structural plasticity (Petreanu and Alvarez-Buylla 2002). By the time of their full maturation, new granule cells are electrophysiologically identical to granule cells generated during development (Petreanu and Alvarez-Buylla 2002), and are activated by functionally relevant olfactory cues (Magavi et al. 2005). New granule cells can survive for periods up to a year or longer (Petreanu and Alvarez-Buylla 2002; Dayer et al. 2003), but many new neurons die within a few weeks of their production. In rodents, only about 50 % of new granule cells survive after the first few weeks in the dentate gyrus and olfactory bulb (Petreanu and Alvarez-Buylla 2002; Winner et al. 2002; Dayer et al. 2003). Research has shown that cell proliferation, neuronal differentiation, and cell survival are influenced by multiple environmental factors (Leuner and Gould 2010), with a large number of stress studies examining effects on cell proliferation.

Research has also preferentially focused on environmental influences on adult neurogenesis in the dentate gyrus with fewer studies focused on the SVZ and olfactory bulb.

2 Stress Inhibits Adult Neurogenesis in the Dentate Gyrus

2.1 Acute Stress Reduces Cell Proliferation

Overall, research suggests that acute exposure to a stressful situation decreases cell proliferation in the dentate gyrus. Acute exposure to a dominant conspecific (social defeat) reduces cell proliferation in the dentate gyrus in mice, tree shrews, and marmosets (Gould et al. 1997, 1998; Yap et al. 2006; Lagace et al. 2010). Similarly, acute exposure to trimethylthiazoline, a natural odor of foxes, predators to rodents, decreases cell proliferation in the rat (Tanapat et al. 2001; Mirescu et al. 2004; Hill et al. 2006; Kambo and Galea 2006). Moreover acute electric shock decreases cell proliferation in the rat (Malberg and Duman 2003). In addition to studies examining cell proliferation, decreases in neuronal differentiation are seen following acute predator odor in the rat (Tanapat et al. 2001), and decreased survival of new granule cells has been observed following acute social defeat and acute predator odor exposure in the rat (Tanapat et al. 2001; Thomas et al. 2007).

The effects of acute physical restraint stress are less clear than the results from the stressors already discussed. Multiple studies show that acute restraint stress lasting 2–6 h does not change cell proliferation in adult rats (Kee et al. 2002; Pham et al. 2003; Rosenbrock et al. 2005). However, one study has shown that 3 h of restraint decreases cell proliferation in the adult rat, yet increases cell proliferation in adult mice (Bain et al. 2004). Because variations in restraint protocols are likely to differentially affect the stress response; comparisons among different restraint studies are often difficult to make (Buynitsky and Mostofsky 2009).

2.2 Chronic Stress Reduces Cell Proliferation, Neuronal Differentiation, and Cell Survival

Chronic stress paradigms normally involve stress induction over the course of days to weeks. Chronic social defeat decreases cell proliferation in the dentate gyrus of tree shrews (Czeh et al. 2001, 2002; Simon et al. 2005), rats (Czeh et al. 2007), and mice (Mitra et al. 2006; Ferragud et al. 2010). In mice, decreases in cell proliferation actually correlate with typical behavior of subordinates (Mitra et al. 2006). Chronic social defeat also decreases the differentiation of new neurons in rats and mice (Ferragud et al. 2010; Van Bokhoven et al. 2011) and reduces the survival of new neurons in tree shrews (Czeh et al. 2002) and rats (Czeh et al. 2007). Similarly, chronic electric shock decreases cell proliferation, neuronal differentiation,

and cell survival in rats (Westenbroek et al. 2004; Dagyte et al. 2009). Chronic restraint stress studies show similar discrepancies as reported above for acute restraint stress studies. Chronic restraint stress has been reported to decrease cell proliferation, neuronal differentiation, and cell survival in rats (Pham et al. 2003; Veena et al. 2011a, b), have no effect on cell proliferation in rats (Rosenbrock et al. 2005; Barha et al. 2011), and even increase survival of new neurons in rats and mice (Snyder et al. 2009b; Barha et al. 2011). Again, differences in age, strain, housing conditions, and type, duration, and frequency of restraint may explain differences in the effect of chronic restraint stress on adult neurogenesis in the dentate gyrus.

Numerous studies indicate that training on various learning paradigms stimulates adult neurogenesis in rats (Gould et al. 1999; Leuner et al. 2004, 2006; Epp et al. 2010). However, when learning is complex or prolonged, it appears to decrease cell proliferation (Aztiria et al. 2007; Dupret et al. 2007). Stress-related novelty in a testing environment decreases cell proliferation even though learning occurs (Ehninger and Kempermann 2006). Finally, increased task difficulty does not affect cell proliferation, but cell survival decreases in a step-wise manner (Epp et al. 2010).

Chronic exposure to multiple mild stressors can serve as an animal model depression, as animals can develop symptoms of learned helplessness over the course of days and weeks. Switching the stressors during the experiment prevents habituation. Stressors commonly used in these types of studies vary greatly and include cold-water swim, immobilization, social isolation, food and water deprivation, chronic illumination, white noise exposure, tail pinch, tilted or shaken cage, and electric shock, although experiments typically do not use all of the above. It should be noted that the specific types of stressors used may be responsible for producing differential effects on adult neurogenesis. In general, cell proliferation is decreased following exposure to multiple stressors (Xu et al. 2007; Surget et al. 2008). Some studies suggest that this effect may be limited to ventral portions of the hippocampus (Elizalde et al. 2010; Tanti et al. 2012), although most earlier studies on this topic did not differentiate between dorsal and ventral parts of the hippocampus. Stress can also diminish differentiation and survival of neurons born before stressor exposure (Lee et al. 2006; Oomen et al. 2007; Dagyte et al. 2011). Together, these studies show that chronic exposure to stressful situations is detrimental to adult neurogenesis in the dentate gyrus in that it decreases cell proliferation, neuronal differentiation, and cell survival.

3 Variations in Age and Sex Complicate the Effects of Stress on Adult Neurogenesis in the Dentate Gyrus

The rates of cell proliferation and adult neurogenesis decrease with age in the dentate gyrus of all species examined, including mice, rats, tree shrews, dogs, marmosets, and macaques (Seki and Arai 1995; Kuhn et al. 1996; Cameron and

McKay 1999; Gould et al. 1999; Simon et al. 2005; Leuner et al. 2007). Stress produces a greater decrease in cell proliferation in the aged tree shrew compared to younger adult tree shrews (Simon et al. 2005), suggesting that older animals may be more susceptible to the negative effects of stress.

Sex differences in baseline adult neurogenesis in the dentate gyrus in control animals have not been reported, although cell proliferation rates vary due to the phase of estrous cycle in female rats (Tanapat et al. 1999), but not in female mice (Lagace et al. 2007). However, females and males have shown differences in how stress affects the production of new neurons. The reduction in cell proliferation in adult male rats after exposure to predator odor is not seen in female rats (Falconer and Galea 2003). Male rats show decreases in the survival of new neurons following chronic electric shock, but increases are seen in female rats (Westenbroek et al. 2004). A recent study suggests that female rats have decreased cell proliferation and survival following chronic restraint, but male rats show no change in cell proliferation, but an increase in cell survival (Barha et al. 2011). These results suggest that male and female animals may respond to stress differently although a clear picture has yet to emerge from these studies.

It should be noted that new neurons in the dentate gyrus mature along a different time scale in adult rats and adult mice. Snyder et al. (2009a) discovered that rats produce a higher number of new cells, and that these new cells mature faster, and show greater activation to functional stimuli than such cells in the mouse. Therefore, potential differences between rats and mice on effects of stress on adult neurogenesis must take into account the inherent differences that exist between rats and mice in baseline conditions.

4 Effects of Stress on Cell production in the SVZ

Research on the effects of various stressors on adult neurogenesis in the SVZ has been limited. Chronic restraint stress has been shown to decrease survival of new neurons in the olfactory bulb, but has no effect on cell proliferation in the SVZ (Kaneko et al. 2006). Chronic forced swim stress decreases the number of progenitor cells in the SVZ (Hitoshi et al. 2007). Chronic exposure to multiple mild stressors reduces the number of immature neurons in the SVZ, although this was measured using an endogenous marker of immature neurons, so it is unclear whether these effects are from decreased proliferation or differentiation into new neurons (Yang et al. 2011). Because chronic exposure to mild multiple stressors does not affect cell proliferation in the SVZ (Silva et al. 2008), the effect from Yang et al. (2011) may be a result of decreased differentiation of new cells into neurons. Conversely, chronic exposure to mild multiple stressors reduces the number of proliferating cells in the SVZ, but it is unclear whether this reflects on decreases in the number of progenitor cells or decreases in the rate of cell proliferation (Mineur et al. 2007).

5 Rewarding Experiences Enhance Adult Neurogenesis in the Dentate Gyrus, Despite Elevated Levels of Stress Hormones

Despite the numerous studies linking stress and elevated glucocorticoid levels to suppressed neurogenesis, there are some experiences that stimulate the release of stress hormones, but enhance adult neurogenesis in the dentate gyrus. For example, running increases stress hormone, or glucocorticoid, levels in the blood (Droste et al. 2003; Makatsori et al. 2003; Stranahan et al. 2006), yet increases cell proliferation, induces neuronal differentiation, and enhances survival of new neurons in the dentate gyrus of both mice (van Praag et al. 1999; Klaus et al. 2009; Snyder et al. 2009b) and rats (Stranahan et al. 2006; Yi et al. 2009). Alcohol-induced impairments in cell proliferation can be rescued by running (Crews et al. 2004). This suggests that running engages mechanisms that protect progenitor cells or new neurons from the detrimental effects of stress-induced release of glucocorticoids. However, running does not change proliferation of new cells in the SVZ or the number of new neurons in the olfactory bulb (Brown et al. 2003; Crews et al. 2004; Schoenfeld et al., unpublished observations). Similarly, housing in an enriched environment can elevate glucocorticoid levels (Benaroya-Milshtein et al. 2004), while increasing neuronal differentiation and cell survival in adult and aged mice (van Praag et al. 1999; Kempermann et al. 2002). Living in an enriched environment also ameliorates stress-induced reductions in cell proliferation, neuronal differentiation, and cell survival in the adult rat (Veena et al. 2009a, b). Again, this suggests some protective mechanism of enriched environment living that allows for neuronal growth despite elevated glucocorticoid levels. However, as observed with running, environmental enrichment has no effect on proliferation of new cells in the SVZ or the number of new neurons in the olfactory bulb (Brown et al. 2003; Plane et al. 2008).

Sexual experience also increases circulating glucocorticoid levels (Bonilla-Jaime et al. 2006). Both acute and repeated sexual experiences increase cell proliferation in the dentate gyrus of adult rats, and chronic sexual experience also enhances survival of new neurons in the dentate gyrus (Leuner et al. 2010). The effect of sexual experience on cell proliferation and neurogenesis in the olfactory bulb has not been examined.

Taken in the context of the negative actions of most stressors on adult neurogenesis, the findings on the positive effects of running, enriched housing, sexual experience, and learning (Leuner and Gould 2010) raise the question of whether these experiences share commonalities that permit neuronal growth despite increased glucocorticoid levels. In this regard, it may be relevant that all of these experiences are rewarding. Rats show anticipatory behavior toward gaining access to an enriched environment (van der Harst et al. 2003). Rats form place preferences for running wheels and mating chambers (Belke and Wagner 2005; Tenk et al. 2009) and can be trained readily to bar press to gain access to wheels or receptive females (Hundt and Premack 1963; Everitt et al. 1987). Intercranial self-

stimulation, a rewarding laboratory experience that taps into circuitry likely engaged in natural reward, results in increased cell proliferation in the dentate gyrus of adult rats and mice as well as elevated glucocorticoid levels (Takahashi et al. 2009). Taken together, these findings suggest that rewarding experience may encourage mechanisms that protect the brain from negative influences of glucocorticoids.

6 Mechanisms of Adult Neurogenesis Inhibition and Stimulation

6.1 Adrenal Steroids

By definition, stress activates the hypothalamic-pituitary-adrenal (HPA) axis, which results in an elevation of glucocorticoids in the blood. Exogenous administration of corticosterone, the main rodent glucocorticoid, results in a decrease in cell proliferation and survival in both the dentate gyrus and SVZ (Cameron and Gould 1994; Wong and Herbert 2006; Lau et al. 2007; Brummelte and Galea 2010a). The inhibition of cell proliferation by corticosterone occurs in both males and females (Brummelte and Galea 2010a) and appears to be independent of reproductive status (Brummelte and Galea 2010b). Conversely, removal of circulating glucocorticoids by adrenalectomy (ADX) promotes cell proliferation and adult neurogenesis in the dentate gyrus (Gould et al. 1992; Cameron and Gould 1994) and SVZ (Guo et al. 2010). Taken together, these findings suggest that the rate of cell proliferation and adult neurogenesis in the dentate gyrus and SVZ of adult rodents can be moderated by circulating levels of glucocorticoids. Since corticosterone injections produce similar effects on adult neurogenesis as stress, it is likely that the stress-induced increases in glucocorticoid levels are responsible for the stress-induced decreases in adult neurogenesis. Indeed, inhibitory effects of fox odor exposure on cell proliferation in the dentate gyrus can be blocked by preventing the stress-induced rise in glucocorticoids (Tanapat et al. 2001). It remains unknown, however, whether these effects are mediated directly via actions of adrenal steroids on progenitor cells or whether they occur indirectly through some unknown factor.

Glucocorticoids bind to two main types of receptors in the brain, the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR) (Reul and de Kloet 1985). Granule cells in the dentate gyrus and olfactory bulb express both types of adrenal steroid receptors (Morimoto et al. 1996). Because, MRs have higher affinity for glucocorticoids than GRs, MRs are more likely to be sensitive to circadian changes in glucocorticoid levels, while GRs are more likely to respond to stress-induced elevations in glucocorticoid levels (de Kloet et al. 1998). Direct activation of MRs through the MR-agonist aldosterone in adult ADX rats enhances cell proliferation and neurogenesis (Fischer et al. 2002), while activation of GRs

through the GR-agonist dexamethasone in adult rats inhibits cell proliferation (Kim et al. 2004), further suggesting that elevation of stress hormones act through GRs to reduce hippocampal neurogenesis.

Although most new neurons express both GR and MR after 4 weeks of maturation, relatively few progenitor cells express adrenal steroid receptors (Cameron et al. 1993a; Garcia et al. 2004). This raises the possibility that adrenal steroid-mediated changes in the rate of cell proliferation in the dentate gyrus occur indirectly. There are several possible mechanisms whereby such an indirect effect might occur. For instance, glucocorticoids might affect neurogenesis by influencing neighboring, more mature, granule neurons. This could occur either by altering the survival of granule cells directly or by affecting their afferent inputs.

With regard to the first possibility, ADX results in massive death of mature granule cells in the dentate gyrus (Sloviter et al. 1989; Gould et al. 1990). Replacement of ADX rats with aldosterone, a mineralocorticoid that binds with high affinity to MRs, is sufficient to protect the dentate gyrus from cell death (Woolley et al. 1991), suggesting that regular activation of MRs is important for the maintenance of the granule cell population. These findings suggest that dying mature granule cells may provide signals that stimulate the proliferation of progenitor cells. In this regard, it is relevant to note that direct destruction of the dentate gyrus, via chemical or mechanical lesion, leads to an increase in the production of new neurons (Gould and Tanapat 1997). The link between cell survival and cell proliferation has not been extensively explored in the dentate gyrus, but several reports suggest that neuronal death can stimulate adult neurogenesis in many other brain regions, including the neocortex and striatum (Gould 2007).

An additional, but not mutually exclusive, possibility is that adult neurogenesis is affected indirectly through adrenal steroid actions on granule cell afferents. Lesion of the entorhinal cortex, one of the main afferent populations to the dentate gyrus, stimulates the production of new neurons (Cameron et al. 1995). Likewise, blockade of NMDA receptors, glutamate receptors involved in perforant path-granule cell synapses, increases adult neurogenesis (Cameron et al. 1995; Maekawa et al. 2009). Moreover, manipulation of cholinergic inputs, via either neurotoxin or pharmacological intervention, alters the rate of adult neurogenesis (Kotani et al. 2006; Frechette et al. 2009). Although not directly explored in the context of adrenal steroids, these afferent populations contain adrenal steroid receptors, and may be one of the intermediate steps between alterations in hormone levels and changes in the production of new neurons.

6.2 Cytokines, Neurotrophins and Neuropeptides

Inflammation decreases cell proliferation in the rodent dentate gyrus (Ekdahl et al. 2003; Monje et al. 2003). Interleukin-1 (IL-1) is a proinflammatory cytokine that is a member of a family of immune factors that communicate inflammation to the

central nervous system. IL-1 incites glucocorticoid release by the adrenal glands (Bernton et al. 1987). Therefore, IL-1 has been implicated in moderating the negative effects of stress on cell proliferation and neurogenesis. Exogenous administration of IL-1β inhibits cell proliferation and neuronal differentiation in the dentate gyrus of adult mice (Goshen et al. 2008; Koo and Duman 2008). Progenitor cells in the SGZ have IL-1 receptors, which decrease cell proliferation when activated (Koo and Duman 2008). Inactivation of IL-1 receptors prevents stress-induced decreases in cell proliferation (Goshen et al. 2008; Ben Menachem-Zidon et al. 2008) suggesting that inflammatory cytokines may also regulate adult neurogenesis. Interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) are also proinflammatory cytokines associated with mediating adult neurogenesis. Adult IL-6 knockout mice show enhanced proliferation and survival of new neurons in the dentate gyrus and SVZ (Bowen et al. 2011) and adult selective TNF receptor knockout mice have promoted neurogenesis in the dentate gyrus (Iosif et al. 2006). Also overproduction of IL-6 impairs adult neurogenesis in the dentate gyrus (Vallieres et al. 2002), further suggesting that inflammatory cytokines can decrease cell proliferation and may be involved in stress-induced deficits in adult neurogenesis. Other inflammatory cytokines are likely to moderate the effects of stress on neurogenesis in the adult.

Neurotrophic factors are important in regulating embryonic neuronal development, and many of these factors are altered after exposure to rewarding experiences that promote adult neurogenesis. Brain-derived neurotrophic factor (BDNF) is a factor in the survival of new neurons in the dentate gyrus (Sairanen et al. 2005), and blocking BDNF decreases the differentiation of new neurons in adult mice (Taliaz et al. 2010). BDNF is released following running (Ying et al. 2005), and is required for enriched environment-induced increases in cell proliferation (Rossi et al. 2006). Vascular endothelial growth factor (VEGF) promotes cell proliferation in the adult rat dentate gyrus (Jin et al. 2002). Chronic stress decreases VEGF expression (Heine et al. 2005). VEGF is necessary for increases in cell proliferation and neuronal differentiation in running mice (Fabel et al. 2003), and for enriched environment-induced cell proliferation, neuronal differentiation, and cell survival in rats (Cao et al. 2004). Hence, VEGF is another potential factor in moderating adult neurogenesis. Insulin-like growth factor 1 (IGF-1) increases cell proliferation in the adult rat dentate gyrus (Aberg et al. 2000) and moderates other positive effects in the brain after running (Carro et al. 2000). Hence, IGF-1 may also be a factor in promoting adult neurogenesis, although research has not investigated the specific role of IGF-1 in the positive neurogenic aspects of reward experiences. No studies have yet examined the roles of BDNF, VEGF, or IGF-1 in sexual experience. Although rewarding behaviors such as running and environmental enrichment do not affect proliferation and neurogenesis in the SVZ, BDNF and VEGF administration also increase proliferation of cells in the SVZ and the number of new neurons in the olfactory bulb (Zigova et al. 1998; Jin et al. 2002; Sun et al. 2006), so growth factors may prevent decreases in SVZ neurogenesis from elevated glucocorticoid levels.

The neuropeptide oxytocin is also worth considering in the context of the effects of rewarding experience on adult neurogenesis. Oxytocin is released in the hippocampus under conditions of social reward, such as during mating (Waldherr and Neumann 2007), and has been shown to buffer against the negative actions of stress (Windle et al. 2004, 2006). Oxytocin has also been shown to stimulate cell proliferation and adult neurogenesis in the dentate gyrus, even under conditions of elevated glucocorticoids and stress (Leuner et al. 2012). These findings raise the possibility that under conditions of reward, oxytocin release into the hippocampus may bypass the suppressant actions of glucocorticoids on progenitor cells. No studies have yet addressed this possibility directly.

Neuropeptide Y (NPY) is another candidate in moderating the effects of rewarding experience on adult neurogenesis. NPY is upregulated in the dentate gyrus of adult mice during running (Bjornebekk et al. 2006), and administration of NPY stimulates adult neurogenesis in the dentate gyrus (Howell et al. 2003, 2005). Because NPY has been associated with behavioral resiliency to stressors (Thorsell et al. 2000; Carvajal et al. 2004; Cohen et al. 2012), it may mediate the positive effects of certain rewarding stressors on adult neurogenesis.

Given that corticotropin releasing factor (CRF) and vasopressin are important modulators of the HPA axis (Holsboer 1999; Aguilera and Rabadan-Diehl 2000), both neuropeptides may be involved in stress-induced decreases in cell proliferation and neurogenesis. Although peripheral injections of vasopressin have not been shown to affect rates of cell proliferation in the dentate gyrus (Leuner et al. 2012), selective vasopressin and CRF receptor antagonists have been shown to reverse the impairment of cell proliferation and neurogenesis in the dentate gyrus of chronically stressed mice (Alonso et al. 2004), suggesting that the neuropeptides CRF and vasopressin may play a role in stress-induced changes in adult neurogenesis, although they may act indirectly through manipulation of the HPA axis.

6.3 Neurotransmitters

Neurotransmitters affect new neuron production and may be involved in the positive and negative effects of different stressors on adult neurogenesis. Excitatory neurotransmitters, such as glutamate, have been shown to have suppressive effects on adult neurogenesis in the dentate gyrus. Activation of glutamatergic NMDA receptors decreases cell proliferation and survival in the adult dentate gyrus, while the use of NMDA antagonists shows the opposite action (Cameron et al. 1995; Gould et al. 1997; Nacher et al. 2003). Consistent with studies on NMDA receptor blockade, lesion of the entorhinal cortex, a major source of glutamatergic input to the granule cells through the perforant path has been shown to increase adult neurogenesis in the dentate gyrus (Cameron et al. 1995). Somewhat surprisingly, a recent study has shown that electrical stimulation of the entorhinal cortex also stimulates adult neurogenesis (Stone et al. 2011) raising the possibility that naturally occurring patterns of entorhinal input typically dampen

new neuron production. Disruption of this pattern, either through removal of the afferent population or artificial electrical stimulation removes this brake and allows a higher rate of adult neurogenesis.

Given the effects that rewarding experiences have on adult neurogenesis, it is perhaps unsurprising that dopamine has been implicated in the regulation of adult neurogenesis. However, mixed results have been reported showing either transient increases or decreases in cell proliferation following dopamine depletion (Hoglinger et al. 2004; Park and Enikolopov 2010). The effect of dopamine on cell proliferation may be receptor-dependent (Veena et al. 2011a, b), and importantly, recent evidence has shown that the new neurons respond differently to dopaminergic activation than mature granule cells, suggesting that dopamine may have a specific role in the maturation and integration of proliferated neurons (Mu et al. 2011). The neurotransmitter serotonin has been shown to also have positive effects on cell proliferation and neurogenesis in the adult. Ablation of serotonin innervation into the dentate gyrus and serotonin receptor antagonists decreases cell proliferation (Brezun and Daszta 2000; Radley and Jacobs 2002). Importantly, the use of antidepressants which selectively block serotonin reuptake can reverse stress-induced decreases in cell proliferation (Qiu et al. 2007; Hitoshi et al. 2007), suggesting that the actions of positive stressors on adult neurogenesis may work as well through serotonergic mechanisms. These neurotransmitters have also been seen to have similar effects on neurogenesis in the SVZ (reviewed in Young et al. 2011), suggesting that common mechanisms may underlie these effects in both regions.

Numerous studies suggest that GABA also plays an important role in adult neurogenesis. In the dentate gyrus, both progenitor cells and new neuroblasts contain functional GABA-A receptors (Wang et al. 2005). Manipulating these receptors alters proliferation of progenitor cells in the SGZ, as administration of GABA-A agonists decrease cell proliferation, and GABA-A antagonists increase cell proliferation (Tokuza et al. 2005). During the early stage of maturation, new cells respond to GABA with excitatory actions (Espósito et al. 2005; Overstreet Wadiche et al. 2005; Ge et al. 2006). New neurons have immature Cl^- channels that cause GABA to have a depolarizing effect during the first few weeks of maturation (Ge et al. 2006; Pathania et al. 2010). This GABAergic depolarization of immature granule cells appears to be important for dendritic growth and neuronal differentiation (Deisseroth et al. 2004; Ge et al. 2006). Blocking GABAergic transmission in immature neurons causes decreased spine density and shorter dendrites upon maturation (Sun et al. 2009). Ge et al. (2006) showed that altering Cl^- channels to make GABA hyperpolarizing in immature neurons truncates dendritic growth and synapse formation. Once new neurons mature, they show typical GABAergic hyperpolarization, and enhanced synaptic potentiation, compared to preexisting neurons (Ge et al. 2006). Interestingly, even after GABA becomes hyperpolarized, new neurons exhibit enhanced LTP compared to older neurons (Ge et al. 2007).

Similar effects of GABA on the development and maturation of new neurons in the adult olfactory bulb have been observed. New GABAergic cells in the

olfactory bulb release GABA into the extracellular space which acts on progenitor cells to dampen cell proliferation (Liu et al. 2005). Increased extracellular GABA slows migration of immature neurons to the olfactory bulb (Bolteus and Bordey 2004; Platel et al. 2008). As observed for new neurons in the dentate gyrus, GABA is depolarizing to immature olfactory bulb neurons and enhances the complexity of their dendritic arbors (Gascon et al. 2006). Blocking GABA-A receptors has been shown to decrease dendritic length of new olfactory bulb neurons (Gascon et al. 2006).

Stress and corticosterone increases dampen GABA release in the hippocampus (de Groote and Linthorst 2007; Grønli et al. 2007; Martisova et al. 2012). Therefore, both acute and chronic stress may affect not only the rate of cell proliferation and neurogenesis in the hippocampus, but GABA signaling as well. Decreased GABA signaling in the dentate gyrus due to stress may have detrimental effects on new neuron maturation and dendritic complexity. On the other hand, running alters GABA-A receptor expression in the dentate gyrus (Hill et al. 2010). Although specific expression in new neurons was not measured, it is reasonable to suggest that running also changes GABA-A receptors in new neurons. Running is known to increase expression of GAD67, the synthetic enzyme for GABA, in the dentate gyrus (Hill et al. 2010), and our recent findings demonstrate that runners have increased expression of vGAT in the dentate gyrus and show a transient increase in GABA release in the hippocampus following stress (Schoenfeld et al., unpublished observations). New neurons born during running in the dentate gyrus mature faster than in a control condition (Snyder et al. 2009b). These results suggest that, opposed to stress, running not only increases the production of new granule cells, but also may foster a GABAergic environment that encourages dendritic growth and heightened maturation in new neurons (Fig. 1). It should be noted that prolonged excitation of new neurons through seizure causes aberrant dendritic growth in new neurons (Jessberger et al. 2007), and aberrant development has been linked to psychiatric disorders such as schizophrenia (Lewis and Levitt 2002). However, running has also been shown to ameliorate behavioral deficits in mouse models of schizophrenia (Wolf et al. 2011); hence, increased dendritic growth of new neurons, is not likely to be severe enough to contribute to pathogenesis.

7 Functional Implications of Changing the Rate of Adult Neurogenesis in the Dentate Gyrus

Since new neurons in the dentate gyrus have been shown to generate action potentials and are activated by hippocampal-dependent behaviors (van Praag et al. 1999; Ramirez-Amaya et al. 2006; Kee et al. 2007; Tashiro et al. 2007; Snyder et al. 2009c; Epp et al. 2011; Snyder et al. 2012), it follows that changes in the rate of adult neurogenesis, either inhibiting or enhancing it, will have a consequence on

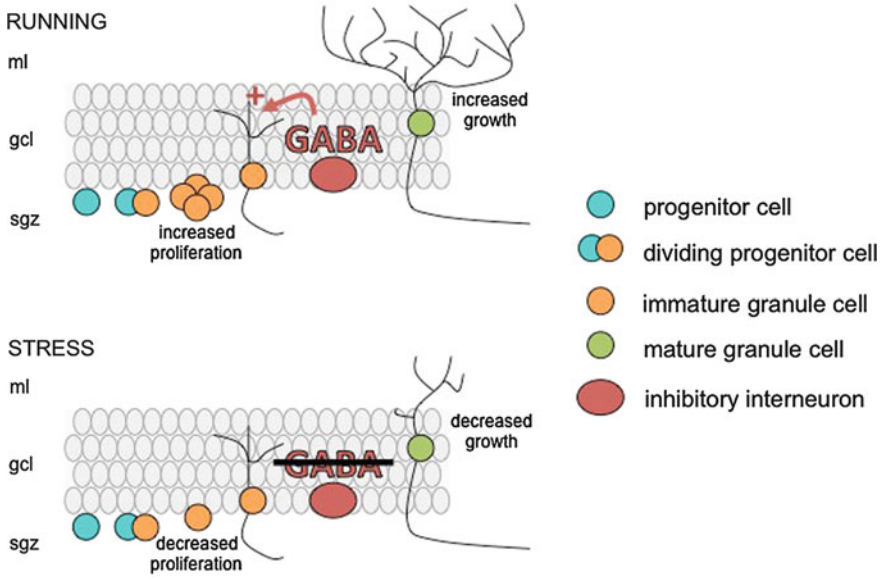

Fig. 1 Schematic diagram of the effects of running and stress on cell proliferation and maturation of new granule cells in the dentate gyrus. Running increases production of new cells and stimulates GABA release. GABA depolarizes immature neurons, fostering dendritic growth and synaptic maturation. Conversely, stress decreases proliferation of new cells and blocks GABA release, resulting in stunted dendritic growth and maturation

hippocampal-dependent functions. The hippocampus contributes to specific types of learning and memory (Moser et al. 1993; Ergorul and Eichenbaum 2004), is important for anxiety regulation (Bannerman et al. 2004; Fanselow and Dong 2010), and modulates feedback of the stress response (Herman et al. 1989; Jacobson and Sapolsky 1991; Herman et al. 1995; Herman and Mueller 2006). All of these functions can be affected by manipulations that are known to change the rate of adult neurogenesis.

Cell proliferation in the dentate gyrus can be knocked down through administration of antiproliferative agents (Shors et al. 2001; Garthe et al. 2009), irradiation (Madsen et al. 2003), and with transgenic models (Garcia et al. 2004). Decreasing neurogenesis in rats results in impaired spatial learning on the Morris water maze, contextual fear conditioning, and trace eye blink conditioning, with no effect on hippocampal-independent cued fear conditioning and delayed eyeblink conditioning (Shors et al. 2001, 2002; Madsen et al. 2003; Snyder et al. 2005; Winocur et al. 2006; Saxe et al. 2006; Warner-Schmidt et al. 2008; Imayoshi et al. 2008; Farioli-Vecchioli et al. 2008; Jessberger et al. 2009). In rats, spatial learning and contextual fear conditioning deficits do not appear until at least 4 weeks following the reduction in new neuron production (Shors et al. 2002; Madsen et al. 2003; Snyder et al. 2005, 2009a; Jessberger et al. 2009), suggesting that the maturation of new neurons is necessary for hippocampal-dependent learning in

rats. In mice, findings are less clear. Studies have shown either deficits or no change in contextual fear conditioning and spatial learning in mice of different strains, sex, and ages, from different time points following ablation (reviewed in Castilla-Ortega et al. 2011). Because new neurons mature more slowly in mice than rats (Snyder et al. 2009a), and different mouse strains exhibit different baseline rates of adult neurogenesis (Kempermann and Gage 2002; Schauwecker 2006; Clark et al. 2011), differences in the effects of deleting adult neurogenesis on learning in mice may be difficult to interpret as general phenomena.

The dentate gyrus has been implicated in mediating pattern separation, the process where highly similar, overlapping representations are dissociated to keep them independent in episodic memory (O'Reilly and McClelland 1994). Adult neurogenesis has been proposed as an important mechanism for pattern separation in the dentate gyrus (Deng et al. 2010). Increasing adult neurogenesis through genetic induction of cell proliferation results in enhanced spatial pattern separation in adult mice (Sahay et al. 2011). Knocking out hippocampal neurogenesis impairs spatial pattern separation in adult mice (Clelland et al. 2009; Tronel et al. 2012). Running-induced increases in cell proliferation are correlated with higher spatial pattern separation in adult mice (Creer et al. 2010). This evidence suggests that stress-reduced adult neurogenesis in the dentate gyrus may have profound effects on hippocampal-dependent memory formation and learning.

Recent evidence indicates that the new neurons play an important role in shutting off the HPA axis after stress (Snyder et al. 2011; Surget et al. 2011). Corticosterone levels are slower to recover to baseline following moderate stress, and the HPA axis is less suppressed by dexamethasone, showing impaired HPA axis feedback, in adult mice without new neurons in the dentate gyrus (Snyder et al. 2011). Although Surget et al. (2011) did not find differences in HPA axis recovery following stress of animals with ablated neurogenesis, they found that the beneficial actions of antidepressants on HPA axis recovery following stress required new neurons. Taken together, these findings suggest that new neurons may play an important role not only in the cognitive functions of the hippocampus, but also in stress regulation. The extent to which stress-induced reductions in adult neurogenesis contribute to increased pathological processes associated with chronic stress, such as anxiety disorders, depression, and HPA axis dysregulation, remains to be determined.

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