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Review

Stress, stress hormones, and adult neurogenesis

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ABSTRACT

The dentate gyrus of the hippocampus continues to produce new neurons throughout adulthood. Adult neurogenesis has been linked to hippocampal function, including learning and memory, anxiety regulation and feedback of the stress response. It is thus not surprising that stress, which affects hippocampal function, also alters the production and survival of new neurons. Glucocorticoids, along with other neurochemicals, have been implicated in stress-induced impairment of adult neurogenesis. Paradoxically, increases in corticosterone levels are sometimes associated with enhanced adult neurogenesis in the dentate gyrus. In these circumstances, the factors that buffer against the suppressive influence of elevated glucocorticoids remain unknown; their discovery may provide clues to reversing pathological processes arising from chronic exposure to aversive stress.

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Contents

Introduction

The granule cell population of the dentate gyrus is produced in three distinct phases occurring during gestation, the early postnatal period and in adulthood. During the embryonic period, new neurons arise from the ventricular zone and migrate across the hippocampal rudiment to populate the incipient dentate gyrus (Schlessinger et al., 1975; Altman and Bayer, 1990). Progenitor cells also migrate into this region and continue to produce new neurons well into the postnatal period; these new granule cells help to form the granule cell layer (Schlessinger et al., 1975; Altman and Bayer, 1990). In young adulthood, progenitor cells are located on the border of the granule cell layer and hilus, a region called the subgranular zone (sgz). These cells divide and produce new granule cells throughout adult life. Although the rate of adult neurogenesis slows considerably with advancing age (Seki and Arai, 1995; Kuhn et al., 1996; Simon et al., 2005; Leuner et al., 2007), some new granule cell production is evident even in the dentate gyrus of the very old.

Adult neurogenesis appears to be a general phenomenon of mammals, being reported in a wide range of species. Although the majority of data on adult neurogenesis come from studies using rats and mice (Cameron and McKay, 1999; Snyder et al., 2009b), new granule cell production has been shown to occur in the dentate gyrus of dogs (Hwang et al., 2007; Cotman and Head, 2008), foxes (Amrein and Slomianka, 2010), tree shrews (Gould et al., 1997; Simon et al., 2005), marmosets (new world monkeys) (Gould et al., 1998; Leuner et al., 2007), macaques (old world monkeys) (Gould et al., 1999a; Perera et al., 2007; Kordower et al., 2010) and humans (Eriksson et al.,

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1998; Knoth et al., 2010). In fact, the only mammals investigated in which adult neurogenesis is either absent or occurs at a very low rate in the dentate gyrus are certain types of bats (Amrein et al., 2007). Taken together, these findings suggest that with rare exceptions, adult neurogenesis is a common feature of the mammalian dentate gyrus. The wide range of species in which adult neurogenesis occurs and the relatively large number of new neurons produced at least in the species for which adequate quantitative data exist (rats, mice, marmosets) suggest that this form of structural plasticity may play an important role in hippocampal function. For this reason, the regulation and function of adult neurogenesis has received focused attention by the Neuroscience community over the past decade.

Numerous studies have attempted to characterize the production of new neurons in the dentate gyrus of adults. Adult neurogenesis can be divided into three main cellular events: cell proliferation, neuronal differentiation, and cell survival (Fig. 1) (Christie and Cameron, 2006). Each of these events has been well-characterized, at least in studies of rodents, and each provides a plastic process that has the potential to be influenced by stress and glucocorticoids.

Cell proliferation refers to the division of progenitor cells located in the sgz of the dentate gyrus. Granule cell progenitors have the morphological characteristics of radial glia (Seri et al., 2001) and express glial fibrillary acidic protein (GFAP), an astroglial marker. Progenitor cells continue to express GFAP at the time of cell proliferation. Neuronal differentiation refers to the selection and emergence of a neuronal fate by some daughter cells. In the dentate gyrus, the majority of new cells differentiate into neurons. In the rodent, the percentage varies in the literature between 80 and 95%, depending on factors such as species, animal age, location of granule cells, and stage of development of cells (Cameron et al., 1993b; Cameron and McKay, 2001; Brown et al., 2003; Snyder et al., 2009a). A smaller percentage (~10) differentiate into glia (Cameron et al., 1993b; Steiner et al., 2004). New glial cells continue to express GFAP while undergoing structural differentiation into mature astrocytes. New neurons stop expressing GFAP and instead express markers for immature neurons, such as doublecortin (DCX), polysialated neuronal cell adhesion molecule (PSA-NCAM) and class III beta-tubulin (Tuj1). While new neurons continue to express TuJ1 as they mature, these cells ultimately stop producing DCX and PSA-NCAM and begin to make proteins specific to mature granule cells, like Neuron specific enolase (NSE), Neuronal nuclei (NeuN) and Calbindin (Fig. 1). It should be noted that the time course of biochemical maturation of new neurons in the dentate gyrus varies among species, even within rodents. For example, new neurons in the adult rat appear to differentiate more rapidly than those in the adult mouse (Snyder et al., 2009a). In addition to biochemical changes that accompany neuronal differentiation, new neurons undergo structural and electrophysiological changes as they transition from immature to mature. Within a few weeks of mitosis, new neurons develop morphological features of granule cells. New granule cells grow characteristic dendritic trees extending toward the molecular layer (Ribak et al., 2004), elaborate axons toward the CA3 region of the hippocampus (Hastings and Gould, 1999; Zhao et al., 2006), and generate action potentials (van Praag et al., 2002). Initially, new neurons respond to GABA, the main inhibitory neurotransmitter of mature granule cells, with excitation (Ge et al., 2006). As new neurons mature, Cl− channels on the granule cell membrane mature and GABA has an inhibitory effect. New neurons also show enhanced

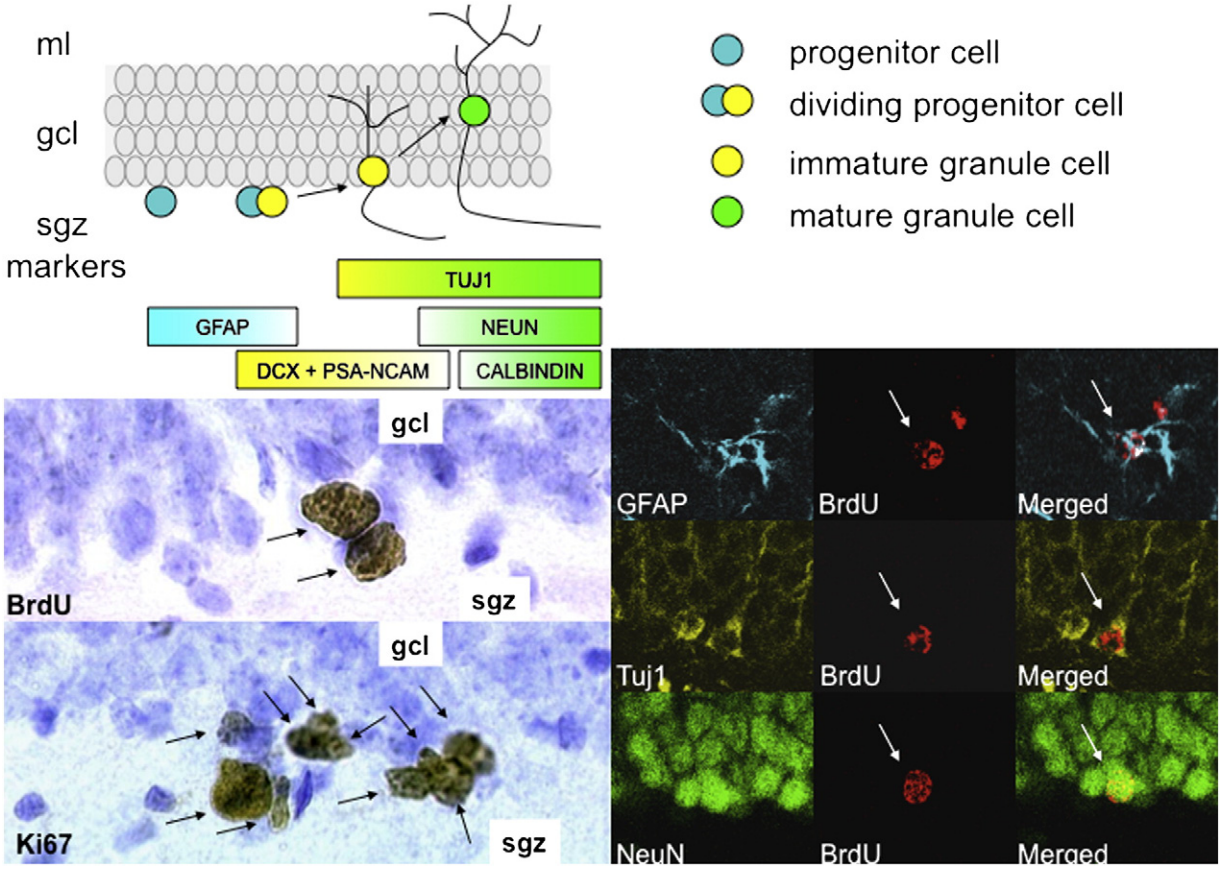

Fig. 1. Top left: schematic diagram of adult neurogenesis in the dentate gyrus of the hippocampus. Progenitor cells in the subgranular zone (sgz) divide and produce daughter cells. Most of these cells differentiate into excitatory granule cells and integrate into the granule cell layer as they differentiate. At different timepoints during their maturation, new cells express specific biochemical markers, listed below the schematic diagram. Photomicrographs (bottom left) show bromodeoxyuridine (BrdU) labeled cells (arrows, top), and Ki67 labeled cells (arrows, bottom). BrdU is an exogenously applied marker that labels cells in S phase, while Ki67 is an endogenous marker of actively cycling cells. Confocal microscopic images (bottom right) show cells labeled with BrdU (red) and a marker of astroglia (GFAP), immature and mature neurons (Tuj1) and mature neurons (NeuN).

synaptic plasticity during maturation (Snyder et al., 2001; Ge et al., 2007) compared to mature granule cells. This lack of inhibition and increased plasticity make new neurons an ideal substrate for influencing hippocampal function.

Cell survival refers to the maintenance of new neurons and their permanent incorporation into the hippocampal circuitry. Some new granule cells survive for very long periods of time (Dayer et al., 2003) but that is not the case for all such cells produced in adulthood. In control rodents, a relatively large percentage of new neurons do not survive past a few weeks (Dayer et al., 2003). The survival of new neurons can be influenced by environmental factors, suggesting that data on cell survival may be confounded by the relatively deprived conditions of standard laboratory life. Studies have shown that all three stages of adult neurogenesis, cell proliferation, neuronal differentiation and cell survival, can be influenced by stress, learning and environmental enrichment (Leuner and Gould, 2010) but the majority of evidence points to stress effects on cell proliferation.

Effects of stress on adult neurogenesis

Acute stressors

Several studies have investigated the effects of stress on adult neurogenesis; these reports have varied in the stressor used and the duration of its application (Table 1). For acute stress, a single episode of stressful experience, some conflicting data exist but the overall result appears to be that stress inhibits adult neurogenesis by lowering the rate of cell proliferation. Subordination stress in adult tree shrews and marmosets results in a decrease in cell proliferation in the dentate gyrus (Gould et al., 1997; 1998). Similar results have been demonstrated for adult mice exposed to social defeat (Yap et al., 2006; Lagace et al., 2010). However, one study reported that acute exposure to a dominant conspecific does not affect cell proliferation in rats, but instead decreases survival of new neurons (Thomas et al., 2007). A likely reason for the lack of effect on cell proliferation in this study was that new cells were labeled with BrdU before the stressful experience so it was not a direct test of stress effects on proliferating cells. Indeed, a large number of studies examining other types of stressors suggest that acute stress can have a suppressive effect on cell proliferation in the dentate gyrus (Table 1).

Exposure to the odors of natural predators activates the HPA axis and produces anxiety-like behavior in rats. Acute stress through exposure to trimethylthiazoline (TMT), a component in fox feces, decreases cell proliferation and differentiation of immature neurons in the dentate gyrus (Hill et al., 2006; Kambo and Galea, 2006; Mirescu et al., 2004; Tanapat et al., 2001). This decrease is not due solely to novel odor experience, as other novel odors do not reduce cell proliferation (Tanapat et al., 2001). One study found no change in cell proliferation following predator odor exposure (Thomas et al., 2006); however, as with the social stress study described previously (Thomas et al., 2007), new cells were labeled during the stressful experience, instead of following it, and therefore is not an accurate test of the effects of stress on cell proliferation.

The effects of physical restraint are somewhat difficult to interpret and not as straight-forward as the effects of social dominance and predator odor on adult neurogenesis. Several studies have suggested that acute restraint lasting 2–6 h has no effect on cell proliferation in adult rats (Kee et al., 2002; Pham et al., 2003; Rosenbrock et al., 2005). However, one study showed that 3 h of restraint decreases cell proliferation in the adult rat (Bain et al., 2004). The same study showed that an increase in cell proliferation was seen in adult mice after acute restraint. It has been suggested that comparisons among different studies using nonstandardized methodologies of physical restraint are impossible because of the variations in intensity, duration, and frequency of restraint across rodent species and strains (Buynitsky and Mostofsky, 2009).

Electric shock to the foot or tail activates the HPA axis and induces anxiety-like behavior in rodents. Acute exposure to electric shock decreases cell proliferation in the dentate gyrus of adult rats (Malberg and Duman, 2003). One study showed a delayed decrease in cell proliferation 7 days following shock after the increases in glucocorticoid levels had returned to baseline (Fornal et al., 2007), suggesting a more complicated relationship may exist between electric shock and cell proliferation.

Chronic stressors

Chronic stress paradigms typically utilize daily stressors over the course of a few days to several weeks. Chronic social stress decreases cell proliferation in tree shrews (Czeh et al., 2001; Czeh et al., 2002; Simon et al., 2005), rats (Czeh et al., 2007), and mice (Ferragud et al., 2010), where subordinate behavior is negatively correlated with cell proliferation rates (Mitra et al., 2006). Chronic social stress also decreases differentiation of new neurons in mice (Ferragud et al., 2010), although this may reflect changes in proliferation and survival of new neurons. Chronic restraint stress has been shown to decrease or not change cell proliferation in adult rats (Pham et al., 2003; Rosenbrock et al., 2005). Chronic restraint stress has also been shown

Table 1
Summary of the effects of different experiences that elevate glucocorticoids on cell proliferation, neuronal differentiation, and cell survival in the dentate gyrus. In general, stressful experiences like social defeat, physical restraint and fox odor exposure have a suppressive effect on adult neurogenesis, while rewarding experiences like running, environmental enrichment, and sexual experience exert a stimulatory effect on adult neurogenesis. NA indicates No available data.

Experience	Cell proliferation	Neuron differentiation	Cell survival
Acute social defeat	Decrease (tree shrew; marmoset)	NA	Decrease (rat)
Chronic social defeat	Decrease (tree shrew; rat; mouse)	Decrease (mouse)	Decrease (tree shrew; rat)
Acute predator odor	Decrease (rat: male) No change (rat: female)	NA	NA
Acute physical restraint	Decrease (rat) No change (rat) Increase (mouse)	NA	NA
Chronic physical restraint	Decrease (rat) No change (rat)	NA	Decrease (rat) Increase (mouse)
Acute electric shock	Decrease (rat)	NA	NA
Chronic electric shock	Decrease (rat)	Decrease (rat)	Decrease (rat: male) Increase (rat: female)
Difficult learning paradigm	Decrease (rat) No change (rat)	NA	Decrease (rat)
Chronic multiple mild stress	Decrease (rat)	Decrease (rat)	Decrease (rat)
Running	Increase (rat; mouse)	Increase (rat; mouse)	Increase (rat; mouse)
Environmental enrichment	Increase (rat; mouse)	Increase (rat; mouse)	Increase (rat; mouse)
Sexual experience	Increase (rat)	NA	Increase (rat)

to reduce survival of new neurons in rats (Pham et al., 2003) but enhance survival of new neurons in mice (Snyder et al., 2009b). Chronic electric shock decreases both cell proliferation and neuronal differentiation (although this latter effect may stem from reduced cell proliferation as well) in adult rats (Dagyte et al., 2009).

Although various studies have suggested that learning increases neurogenesis in the adult dentate gyrus (Gould et al., 1999b; Leuner et al., 2004; 2006; Epp et al., 2010), when learning is difficult or stressful, it can have a negative impact on cell proliferation (Aztiria et al., 2007). Stress related to using novel testing paradigms decreases cell proliferation even though learning occurs (Ehninger and Kempermann, 2006). Step-wise increases in task difficulty do not change cell proliferation, but decrease survival of new neurons in the adult rat dentate gyrus (Epp et al., 2010).

Chronic use of multiple mild stressors is an animal model of depression, as animals tend to develop symptoms of learned helplessness over the course of days and weeks. Mild stressors commonly used 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. Multiple mild stressors decrease cell proliferation directly following a stressor, although this effect can be short-lived (Xu et al., 2007). Neurons born prior to mild stressor exposure show diminished differentiation and survival (Lee et al., 2006; Oomen et al., 2007). Overall, the results suggest that chronic stressful experience decreases adult neurogenesis by influencing cell proliferation, neuronal differentiation and cell survival, although the effects vary depending on the study perhaps because of differences in stressor, species or strain.

Age, species, and sex differences

Adult neurogenesis declines steadily with age in the hippocampus of every species in which this has been examined, including rats, mice, tree shrews, dogs and marmosets (Seki and Arai, 1995; Kuhn et al., 1996; Cameron and McKay, 1999; Simon et al., 2005; Leuner et al., 2007). Some evidence suggests that stress effects on adult neurogenesis may be greater in the aged animal than the young animal. There is a greater decrease in cell proliferation of aged tree shrews compared to young adult tree shrews following social stress (Simon et al., 2005).

Baseline differences in adult neurogenesis in the dentate gyrus exist among species. Most notably, there is greater production of new neurons in rats compared to mice; new neurons differentiate faster and are more functionally significant in the hippocampus of rats than mice (Snyder et al., 2009a). As mentioned above, acute restraint stress decreases cell proliferation in rats but increases cell proliferation in mice (Bain et al., 2004). Species differences in adult neurogenesis may alter the effects of stress on adult neurogenesis.

Robust sex differences in baseline adult neurogenesis in the dentate gyrus have not been reported, although estrous cycle differences exist in female rats (Tanapat et al., 1999), but not in female mice (Lagace et al., 2007). However, females and males may differ in how adult neurogenesis is affected by stressful experiences. The reduction in cell proliferation in adult male rats after fox odor exposure is not seen with female rats (Falconer and Galea, 2003). Male rats show decreases in the survival of new neurons following chronic electric shock, but female rats show increases in the survival of new neurons following chronic electric shock (Westenbroek et al., 2004). These results only appear during periods of social isolation. When rats are group-housed, the differences disappear between males and females. Prenatal stress can affect baseline neurogenesis rates when pups mature to adulthood. Male rats that were stressed prenatally have suppressed baseline survival of new neurons, while there is no change in female rats that were stressed prenatally (Zuena et al., 2008). Early weaning results in greater suppression of cell proliferation and survival of new neurons in adult male versus adult female mice (Kikusui et al., 2009). These results suggest that differences across age, species and sex exist in various effects of stressful experiences on adult neurogenesis.

Mechanisms underlying stress effects on adult neurogenesis

Adrenal steroids

Stress is accompanied by HPA activity, which results in the release of glucocorticoids into the blood. In general, glucocorticoids appear to inhibit adult neurogenesis in the dentate gyrus. Exogenous administration of corticosterone to rodents produces a decrease in the number of proliferating cells and surviving new granule neurons (Cameron and Gould, 1994; Wong and Herbert, 2006; Brummelte and Galea, 2010a). The suppressive action of corticosterone on cell proliferation seems to occur independent of sex (Brummelte and Galea, 2010a) and reproductive status (Brummelte and Galea, 2010b). By contrast to the negative actions of glucocorticoids on adult neurogenesis, removal of the adrenal glands by adrenalectomy (ADX) stimulates cell proliferation and adult neurogenesis in the dentate gyrus (Gould et al., 1992; Cameron and Gould, 1994). Taken together, these findings suggest that the rate of cell proliferation and adult neurogenesis in the dentate gyrus of adult rodents can be regulated by the levels of circulating glucocorticoids. Since glucocorticoid 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 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.

Adrenal steroid effects: Direct or indirect?

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 express both subtypes of adrenal steroid receptors. Because MRs have higher affinity for glucocorticoids than GRs, MRs are more sensitive to circadian changes in glucocorticoids while GRs respond more to stress-induced elevations in glucocorticoids (de Kloet et al., 1998).

Although most new neurons express both GR and MR after 4 weeks of maturation, relatively few progenitor cells express glucocorticoid receptors (Cameron et al., 1993a; Garcia et al., 2004a). 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 could 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 normal dentate gyrus function. 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). It is possible that dying cells produce a chemical signal that is mitogenic. Alternatively, mature intact neurons may provide an anti-mitotic signal that is lost when cells die leading to an increase in cell proliferation. The specific signals, however, remain unknown.

An additional, but not mutually exclusive, possibility is that 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; Fréchette 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.

Cytokines

Exposure to certain types of stressors increases the levels of cytokines such as interleukin-1 (IL-1) in the periphery and brain (Grippo et al., 2005; Deak et al., 2005). Increased levels of IL-1 can further sensitize HPA axis responses to subsequent stressor exposures (Schmidt et al., 2003; Johnson et al., 2004). Interleukin-1 (IL-1) is a pro-inflammatory cytokine which is a member of a family of immune factors that communicate inflammation to the central nervous system. IL-1 works to stimulate glucocorticoid release by the adrenal glands (Bernton et al., 1987). This pathway raises the possibility that under certain conditions, stress may inhibit adult neurogenesis by stimulating glucocorticoid release through elevated IL-1. Inflammation, a condition associated with increased IL-1, has been shown to reduce cell proliferation and survival of new neurons in the dentate gyrus of the adult rat (Ekdahl et al., 2003). Administration of IL-1β itself decreases cell proliferation and differentiation of new neurons in the adult mouse dentate gyrus (Goshen et al., 2008; Koo and Duman, 2008). In vivo and in vitro studies suggest that progenitor cells in the sgz have IL-1 receptors and that activation of these receptors decreases cell proliferation (Koo and Duman, 2008). Inactivation of IL-1 receptors via transgenic manipulations (Goshen et al., 2008) or pharmacological antagonists (Ben Menachem-Zidon et al., 2008) blocks stress-induced depressive-like behaviors and decreased cell proliferation in the dentate gyrus. These findings suggest IL-1 may underlie the stress-induced decrease in adult neurogenesis in the dentate gyrus but since available evidence suggests that not all stressors activate this pathway, the mechanism is unlikely to be universal.

Paradoxical effects of rewarding experience on adult neurogenesis

Despite the various experiences that activate the HPA axis and produce a suppressive effect on adult neurogenesis (Table 1), there are some behaviors that activate the HPA axis but are associated with increased rates of adult neurogenesis. For example, physical exercise activates the HPA axis and increases glucocorticoid levels in the blood (Droste et al., 2003; Makatsori et al., 2003; Stranahan et al., 2006). Physical exercise also enhances cell proliferation, neuronal differentiation and survival of new neurons in the dentate gyrus of the adult mouse (Klaus et al., 2009; van Praag et al., 1999; Snyder et al., 2009b) and rat (Stranahan et al., 2006; Yi et al., 2009). Running also rescues cell proliferation in the dentate gyrus from alcohol-induced inhibition (Crews et al., 2004). This suggests that running engages mechanisms that protect progenitor cells or new neurons from the detrimental effects of elevated glucocorticoids.

Housing in an enriched environment can increase adrenal gland size (Moncek et al., 2004) and circulating glucocorticoid levels (Benaroya-Milshtein et al., 2004). However, environmental enrichment living increases differentiation and survival of new neurons (van Praag et al., 1999) and buffers against age-related decreases in neurogenesis (Kempermann et al., 2002) in adult mice. Enriched environment living also rescues stress-induced decreases in cell proliferation, neuronal differentiation and survival of new neurons in the adult rat (Veena et al., 2009a; 2009b). Again, this suggests some protective mechanism of enriched environment living that allows for neuronal growth despite elevated glucocorticoid levels.

Sexual experience also increases circulating glucocorticoid levels (Bonilla-Jaime et al., 2006). Acute sexual experience increases cell proliferation in the dentate gyrus of adult rats (Leuner et al., 2010). Chronic sexual experience increases cell proliferation and adult neurogenesis in the dentate gyrus (Leuner et al., 2010). Learning has also been shown to increase glucocorticoid levels (Leuner et al., 2004) and various studies have shown that training on certain types of learning tasks increases adult neurogenesis (Leuner et al., 2006).

Taken in the context of the negative actions of glucocorticoids on adult neurogenesis, these findings are puzzling and raise the question of whether running, enriched environment living, sexual experience and learning have a common characteristic that permits neuronal growth despite a negative hormonal milieu. In this regard, it may be relevant that all of these experiences have a hedonic component. Running, environmental enrichment, and sexual experience are rewarding to rodents. Rats form place preferences for running wheels and mating chambers (Belke and Wagner, 2005; Tenk et al., 2009) and will bar press to gain access to wheels or receptive females (Everitt et al., 1987; Hundt and Premack, 1963). Rats show anticipatory behavior toward gaining access to an enriched environment (van der Harst et al., 2003). Other types of rewarding experiences can also promote adult neurogenesis, as intracranial self-stimulation enhances cell proliferation in the dentate gyrus of adult rats and mice despite elevated glucocorticoid levels (Takahashi et al., 2009). The rewarding nature of these experiences may provide some clues about mechanisms that protect the brain from the negative influences of high levels of glucocorticoids.

Rewarding social experiences are associated with the release of factors that may serve to protect against elevated glucocorticoids and actually promote neuronal growth. Among these are neuropeptides, such as endogenous opioids and oxytocin and the neuromodulator dopamine. Some evidence suggests that each of these factors is capable of stimulating the production of new neurons in the hippocampus (Morton et al., 2009; Höglinger et al., 2004; Winner et al., 2009; Lloyd et al., 2010; Koehl et al., 2008; Persson et al., 2003). It is also possible that neurotrophic factors play a role in buffering the brain from the suppressive actions of elevated glucocorticoids. For example, brain-derived neurotrophic factor (BDNF) is increased following running (Ying et al., 2005). BDNF is a factor in survival of new neurons (Sairanen et al., 2005), and blocking BDNF decreases differentiation of new neurons in the adult mouse dentate gyrus (Taliaz et al., 2010). BDNF is required for enriched environment-induced increases in cell proliferation in adult mice (Rossi et al., 2006). Vascular endothelial growth factor (VEGF) administration also increases cell proliferation in the dentate gyrus of the adult rat (Jin et al., 2002). VEGF is required for running-induced increases in cell proliferation and differentiation of new neurons in adult mice (Fabel et al., 2003), and for enriched environment-induced cell proliferation, differentiation and survival of new neurons in adult rats (Cao et al., 2004). Chronic stress decreases VEGF expression (Heine et al., 2005), so VEGF is another potential factor in mitigating adult neurogenesis. Insulin-like growth factor 1 (IGF-1) administration increases cell proliferation in the dentate gyrus of the adult rat (Aberg et al., 2000), mediates positive neural changes in the brain following exercise (Carro et al., 2000), and is increased following antidepressant

treatment (Khawaja et al., 2004), which is known to stimulate cell proliferation. Therefore, IGF-1 may also be a factor in the paradoxical effects of rewarding experiences on adult neurogenesis, although no direct evidence has supported this yet. No studies have yet examined the roles of BDNF, VEGF, or IGF-1 in sexual experience.

Potential consequences of stress-induced changes in adult neurogenesis

The influence of elevated glucocorticoid levels and exposure to stressful experiences on adult neurogenesis raises the question of what is the functional impact of changing the rate of new neuron production in the adult hippocampus. Since the hippocampus is important for certain types of learning and memory (Moser et al., 1993; Ergorul and Eichenbaum, 2004), anxiety regulation (Bannerman et al., 2004) and shutting off the HPA axis (Herman et al., 1989; Jacobson and Sapolsky, 1991; Herman et al., 1995; Herman and Mueller, 2006), these present possible functions that may be affected by changes in adult neurogenesis. It should be emphasized at the outset of this discussion, that stress and glucocorticoids exert effects elsewhere in the hippocampus, including on the pyramidal cell population (Fig. 2). These effects, which include changes in the biochemistry, electrophysiology and structure of neurons in the CA fields, are likely to contribute to stress-induced changes in hippocampal function. The extent to which changes in adult neurogenesis, through the connections of the granule cell population to other neuronal populations (e.g., CA3 pyramidal neurons, hilar mossy cells), participate in stress-induced changes throughout the hippocampus remains unknown. However, stress effects on processes other than adult neurogenesis should be kept in mind when attempting to assess the functional impact of changes in new neurons.

Most studies investigating the functional impact of new neurons in the hippocampus have tended to focus on their potential role in learning and memory. Antiproliferative agents (Shors et al., 2001; Garthe et al., 2009), irradiation (Madsen et al., 2003), and transgenic models (Garcia et al., 2004b), all ways to reduce cell proliferation in the hippocampus, have been shown to produce changes in cognitive tasks associated with the hippocampus. Decreased hippocampal neurogenesis has no effect on hippocampal-independent cued fear conditioning, but impairs hippocampal-dependent context fear conditioning (Winocur et al., 2006; Saxe et al., 2006; Warner-Schmidt et al., 2008; Imayoshi et al., 2008; Farioli-Vecchioli et al., 2008). In rats, context fear deficits do not appear until at least 4 weeks following neurogenesis ablation (Snyder et al., 2009a), suggesting that a certain degree of new neuron maturation is critical for context fear conditioning in rats. In the Morris water maze paradigm, rats show deficits in lasting retention of spatial information at least 4 weeks following ablation of hippocampal neurogenesis, but not before (Shors et al., 2002; Madsen et al., 2003; Snyder et al., 2005; Jessberger et al., 2009). In mice, the picture is less clear. Studies have shown deficits or no change in context fear conditioning and Morris water maze learning in mice of various strains, gender, and ages, from different time points following ablation (Raber et al., 2004; Rola et al., 2004; Saxe et al., 2006; Meshi et al., 2006; Imayoshi et al., 2008; Dupret et al., 2008; Zhang et al., 2008; Farioli-Vecchioli et al., 2008; Deng et al., 2009; Garthe et al., 2009; Ko et al., 2009, Kitamura et al., 2009; Snyder et al., 2009a; Goodman et al., 2010), suggesting that strain, gender, and age-related differences in mice may exist in the

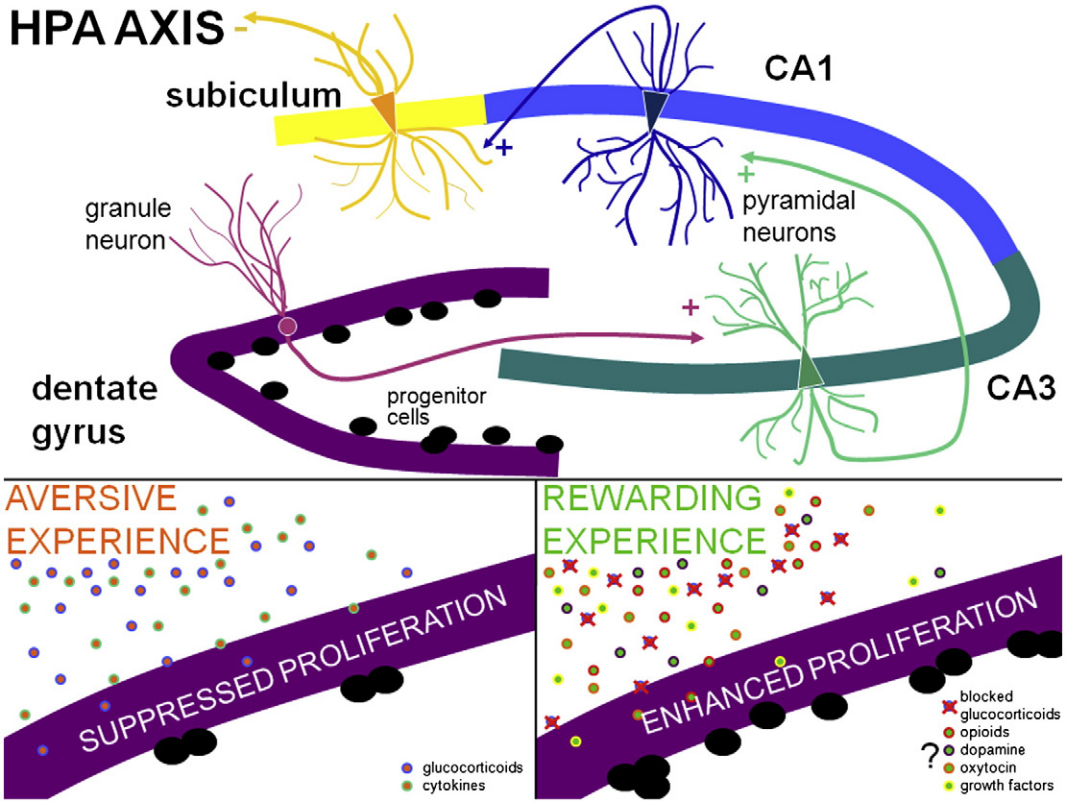

Fig. 2. Schematic diagram of the effects of stress and glucocorticoids on principal cell types in the hippocampus. Stress causes release of glucocorticoids which bind to receptors on all principal cell types in the hippocampus. The dentate gyrus contains granule cells which have excitatory connections with pyramidal cells of the CA3 region. CA3 pyramidal cells have excitatory connections to pyramidal cells in the CA1 region, which have excitatory connections to pyramidal cells in the subiculum, the main output of the hippocampus. Pyramidal cells in the subiculum ultimately exert an inhibitory influence over the HPA axis, helping the system to return to baseline after stress. Aversive experiences are known to inhibit adult neurogenesis in the dentate gyrus potentially through elevated levels of glucocorticoids and cytokines. Rewarding experiences, on the other hand, are known to stimulate adult neurogenesis in the dentate gyrus despite elevated levels of glucocorticoids. Factors that protect against elevated glucocorticoids under conditions of rewarding experience remain unknown; some potential candidates include opioids, dopamine, oxytocin and growth factors.

time course for new neuron maturation and integration or reactions to different ablation techniques.

Recently, it has been argued that classical hippocampal-dependent learning paradigms do not accurately reflect the role of the dentate gyrus (Deng et al., 2010). Computational work suggests that the dentate gyrus may be involved specifically in pattern separation, the process where highly similar, overlapping cortical representations are separated to keep them independent in episodic memory (O'Reilly and McClelland, 1994). Some evidence suggests that new neurons may be important for the ability of the dentate gyrus to separate patterns (Deng et al., 2010). Increased adult neurogenesis has been linked to enhanced spatial pattern separation in mice (Creer et al., 2010). Conversely, ablation of new neurons in the dentate gyrus produces deficits in spatial pattern separation in mice (Clelland et al., 2009). Taken together, the available evidence suggests that stress-reduced adult neurogenesis in the dentate gyrus may have profound effects on hippocampal-dependent memory formation and learning, although the specific functions affected remain undetermined.

More recent studies have linked adult neurogenesis with anxiety regulation and feedback of the stress response. Experimental manipulations associated with reduced number of new neurons in the dentate gyrus are associated with increased anxiety-like behavior (Bergami et al., 2009; Revest et al., 2009). Likewise, reduced adult neurogenesis is associated with impaired modulation of the HPA axis; corticosterone levels show a delayed return to baseline after stress in mice lacking new neurons. Furthermore, reduced neurogenesis is associated with impaired responsiveness of the HPA axis to a dexamethasone suppression test (Snyder et al., 2010). 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 its anxiety and stress regulatory functions. The extent to which stress-induced reductions in adult neurogenesis contribute to increased pathological processes associated with chronic stress, such as anxiety and HPA axis dysregulation, remains to be determined.

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