Stress and Hippocampal Neurogenesis

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The dentate gyrus of the hippocampal formation develops during an extended period that begins during gestation and continues well into the postnatal period. Furthermore, the dentate gyrus undergoes continual structural remodeling in adulthood. The production of new granule neurons in adulthood has been documented in a number of mammalian species, ranging from rodents to primates. The late development of this brain region makes the dentate gyrus particularly sensitive to environmental and experience-dependent structural changes. Studies have demonstrated that the proliferation of granule cell precursors, and ultimately the production of new granule cells, are dependent on the levels of circulating adrenal steroids. Adrenal steroids inhibit cell proliferation in the dentate gyrus during the early postnatal period and in adulthood. The suppressive action of glucocorticoids on cell proliferation is not direct but occurs through an NMDA receptor-dependent excitatory pathway. Stressful experiences, which are known to elevate circulating levels of glucocorticoids and stimulate hippocampal glutamate release, inhibit the proliferation of granule cell precursors. Chronic stress results in persistent inhibition of granule cell production and changes in the structure of the dentate gyrus, raising the possibility that stress alters hippocampal function through this mechanism. This review considers the unusual developmental profile of the dentate gyrus and its vulnerability to environmental perturbations. The long-term impact of developmental events on hippocampal function is considered. Biol Psychiatry 1999;46: 1472–1479 © *1999 Society of Biological Psychiatry*

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Development of the Dentate Gyrus

The dentate gyrus of the hippocampal formation is formed during an extended period that begins in gestation and continues well into the postnatal period. In all mammalian species examined, the production of granule neurons, the principal neuron type of the dentate gyrus, begins during the embryonic period (Altman and Bayer 1990; Bayer 1980). Granule cell precursors arise from the wall of the lateral ventricle and migrate across the hippocampal rudiment to reside in the incipient dentate gyrus. The majority of these cells retain the ability to divide. In rodents, granule cell genesis peaks shortly after birth, during the first postnatal week (Bayer 1980; Schlessinger et al 1975) At this time, the granule cell layer is formed from progenitor cells that reside in the dentate gyrus itself. These cells divide and produce daughter cells that form the granule cell layer along the following gradients: outside-in, suprapyramidal-infrapyramidal, and temporal-septal (Bayer 1980; Schlessinger et al 1975). Thereafter, the production of new granule neurons tapers off but does not cease. From the end of the second postnatal week into adulthood, granule cell precursors that are now located in the hilus and on the border of the granule cell layer and hilus, a region called the subgranular zone, divide and produce daughter cells, the majority of which differentiate into mature granule neurons. In primates, the structure of the granule cell layer is formed during gestation, but granule cell genesis continues postnatally (Nowakowski and Rakic 1981; Rakic 1985).

Granule Cell Genesis in Adulthood

The first report of neuron production in the dentate gyrus of adult brains was published more than 30 years ago by Altman and Das (1965). Using ^{3}H-thymidine autoradiography to label proliferating cells and their progeny, these investigators demonstrated that new cells are produced in the dentate gyrus of the adult rat (Altman and Das 1965). These new cells were incorporated into the granule cell layer and had the nuclear morphology of mature granule neurons. Since this early report, numerous studies have provided further support that these new cells become neurons. It has been shown that adult-generated cells in the dentate gyrus of rats develop the morphological characteristics of granule cells, receive synaptic input, extend axons into the mossy fiber pathway, and express a number of markers of mature neurons (Figure 1) (Cameron et al 1993b; Gould and Tanapat 1997; Gould et al 1999; Hastings and Gould 1999; Kaplan and Bell 1983; Kaplan and Hinds 1977; Stanfield and Trice 1988). These studies were performed exclusively in the rodent brain, how-

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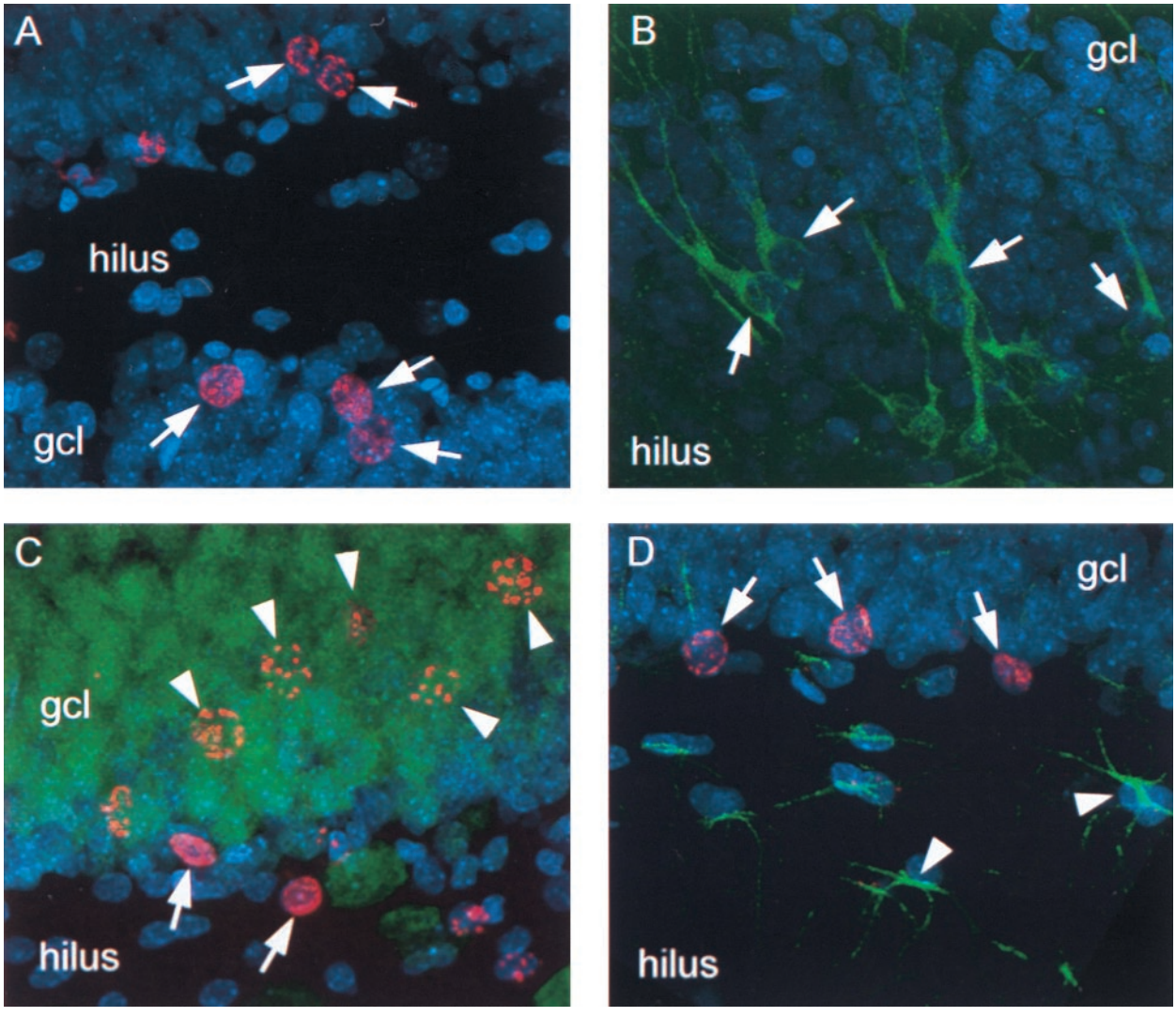

Figure 1. Confocal laser scanning microscopic images of new cells in the dentate gyrus (gcl = granule cell layer). **(A)** BrdU-labeled cells (arrows) in the granule cell layer of an adult rat. **(B)** Cells that are immunoreactive for TOAD-64 (arrows), a marker of immature neurons, in the granule cell layer of an adult macaque. **(C)** BrdU-labeled cells that express NeuN (arrowheads), a marker of mature neurons, in the granule cell layer of a rat. Arrows indicate BrdU-labeled cells that are not immunoreactive for NeuN. **(D)** BrdU-labeled cells (arrows) in the granule cell layer of a rat that are not immunoreactive for GFAP, a marker of astroglia. GFAP positive cells that are not labeled with BrdU are indicated by arrowheads.

ever, and previously published reports showing no convincing evidence of neurogenesis in the brains of adult Old World monkeys, *Macaca mulatta* (Eckenhoff and Rakic 1988; Rakic 1985), suggested that this phenomenon may be biologically insignificant. Nonetheless, in the past few years, evidence has been growing to support the view that adult neurogenesis in the dentate gyrus is a feature of all mammalian species. The production of a substantial number of new neurons in the dentate gyrus in adulthood has been demonstrated in a variety of mammalian species, including rats (Figure 1), mice, tree shrews, marmosets (New World monkeys), macaques (Old World monkeys) (Figure 1), and humans (Cameron et al 1993b; Eriksson et al 1998; Gould et al 1997; Gould et al 1998; Gould et al 1999; Kempermann et al 1997). In addition to adding information regarding the species that undergo granule neuron production in adulthood, many recent studies have indicated that the number of neurons generated in adulthood is higher than previously observed. Use of bromodeoxyuridine (BrdU), a thymidine analog, to label proliferating cells and their progeny, has enabled the estimation of the total number of new cells produced. Unlike ^{3}H-thymidine autoradiography, which underestimates the number of new cells produced (because it only allows for detection of ^{3}H in the top 3–4

μm of a tissue section), stereological analyses can be performed on tissue labeled with BrdU, a nonisotopic technique. Using BrdU labeling combined with cell type–specific markers, recent studies have shown that several thousand new neurons are produced every day in the dentate gyrus of adult rats (Gould et al 1999; Tanapat et al 1999).

These observations suggest that late-generated cells play an important role in hippocampal function.

The extended period of granule cell genesis may render the dentate gyrus unusually sensitive to experience-dependent structural changes. The proliferation of granule cell precursors and the ensuing developmental events, such as dendritic differentiation, axon formation, and synaptogenesis, represent several dynamic processes that could be altered by postnatal experience. Thus, the developmental pattern of the dentate gyrus may allow the use of experiential cues to shape its structure. This ability could enable the continual restructuring of this area according to the current environment, thus affording important adaptive plasticity. On the other hand, the extended period of development might render the dentate gyrus particularly sensitive to environmental perturbations that may adversely alter hippocampal structure and function.

Studies performed over the past several years have identified endocrine, neural, and experiential factors that regulate the production and survival of late-generated neurons in this brain region. Although most studies examining the regulation of postnatal (including adult) neurogenesis have been performed in rats, the available data suggest that the production of new neurons is affected by the same factors in rodents and primates.

Effects of Adrenal Steroids on Granule Cell Production

Throughout postnatal life, glucocorticoids appear to exert suppressive effects on cell proliferation in the dentate gyrus. Basal levels of adrenal steroids are inversely correlated with the rate of cell proliferation in the dentate gyrus (Sapolsky and Meaney 1986; Schlessinger et al 1975). Shortly after birth in the rat, adrenal steroid levels decrease and remain low for the first two postnatal weeks of life. This phase, called the stress hyporesponsive period, coincides with the period of maximal granule cell production in the dentate gyrus (Schlessinger et al 1975). At the end of this period, when adrenal steroid levels rise, granule cell production slows to the rate that is observed in adulthood (Cameron et al 1993b; Sapolsky and Meaney 1986; Schlessinger et al 1975). The decline in the rate of cell proliferation after the stress hyporesponsive period is probably the result of both a diminution in the number of progenitor cells and an increase in the levels of glucocorticoids. Basal levels of adrenal steroids are further elevated in aged rodents and primates (Sapolsky et al 1985). Consistent with the negative regulation of neurogenesis observed in young adult rats by adrenal steroids, the rate of granule cell production is diminished in aged rats (Kuhn et al 1996) and macaques (Gould et al 1999).

Some evidence suggests that these naturally occurring correlations reflect the inhibition of cell proliferation by glucocorticoids. Experimental elevations in the levels of the glucocorticoid corticosterone, the primary glucocorticoid present in rats, diminish the number of proliferating cells in the dentate gyrus during the stress hyporesponsive period, when adrenal steroid levels are naturally low (Gould et al 1991). Likewise, treatment of adult rats with corticosterone also diminishes the proliferation of granule cell precursors (Cameron and Gould 1994). Consistent with these observations, removal of adrenal steroids after the stress hyporesponsive period stimulates the proliferation of granule cell precursors and ultimately the production of new granule neurons (Cameron and Gould 1994; Gould et al 1992). Consistent with these observations, removal of adrenal steroids stimulates the proliferation of granule cell precursors during adulthood and in aging (Cameron and McKay 1999).

Adrenal Steroids Inhibit Cell Proliferation through an NMDA-Receptor-Mediated Excitatory Pathway

Although a regulatory role of adrenal steroids in granule cell production has been well established, the absence of either Type 1 or Type 2 adrenal steroid receptors in most granule cell precursors (Cameron et al 1993a) suggests that the effects of glucocorticoids on cell proliferation occur through another factor. A number of studies suggest that the proliferation of granule cell precursors in the dentate gyrus is regulated by NMDA-receptor-mediated excitatory input. During the time of maximal granule cell genesis in rats, blockade of NMDA receptors enhances the proliferation of granule cell precursors (Gould et al 1994). In adulthood, treatment with either competitive or noncompetitive NMDA-receptor antagonists has a similar effect on cell proliferation in the rodent and tree shrew dentate gyrus. Conversely, activation of NMDA receptors inhibits cell proliferation in the dentate gyrus in adulthood (Cameron et al 1995). The granule cell population receives a major excitatory input from the entorhinal cortex via the perforant path. Transmission across this pathway can involve NMDA-receptor activation, suggesting that perforant path input may participate in the suppression of cell proliferation in the dentate gyrus. Indeed, lesion of the entorhinal cortex has a similar effect on cell proliferation as blockade of NMDA receptors (i.e., enhancement of cell

proliferation in the dentate gyrus during adulthood; Cameron et al 1995).

Stressful Experiences Suppress the Production of Granule Cells during Development and in Adulthood

The suppressive effects of glucocorticoids and NMDA receptor activation on granule cell genesis suggest that stressful experiences, which are known to elevate levels of circulating glucocorticoids and stimulate hippocampal glutamate release in adulthood (Moghaddam et al 1994), naturally inhibit cell proliferation in the dentate gyrus. During the stress hyporesponsive period, rat pups exhibit a diminished response to most stressors that are known to increase circulating levels of adrenal steroids in adult animals (Sapolsky and Meaney 1986). It has recently been demonstrated, however, that male rat pups exhibit an increase in circulating levels of the adrenal steroid corticosterone following acute exposure to the odor of an unfamiliar adult male (adult males are a natural predator of rat pups) (Tanapat et al 1998). Using this paradigm, it has been shown that a single exposure to a stressful experience during the stress hyporesponsive period results in a significant decrease in the proliferation of granule cell precursors in the developing dentate gyrus (Tanapat et al 1998).

The suppression of cell proliferation by stress during adulthood has been demonstrated as well. Previously, it has been shown that an acute stressful experience decreases the number of adult-generated neurons produced in the adult dentate gyrus in a number of different species including rat (Galea et al 1996), tree shrew (Gould et al 1997), and marmoset (Gould et al 1998). In adult rats, exposure to predator odor elicits a stress response characterized by increased adrenal steroid levels (Vernet-Maury et al 1984) and excitation in the dentate gyrus (Heale et al 1994; Sgoifo et al 1996). A single brief exposure to trimethyl thiazoline, the main component of fox feces, rapidly suppresses the proliferation of cells in the dentate gyrus (Galea et al 1996). Similar observations have been made in studies that examined the effect of social stress in nonrodent species. In tree shrews, the introduction of two adult same-sex conspecifics immediately results in the establishment of an enduring dominant-subordinate relationship (von Holst 1972). During this time, the subordinate exhibits physiological and behavioral indicators of stress, including increased cortisol levels, increased heart rate, a reduced sphere of activity, hypervigilance, alarm cries, and tail ruffling (von Holst 1972). Once the dominant-subordinate relationship has been established, the subordinate animal will exhibit an immediate stress response during subsequent encounters with the dominant animal (von Holst 1972). A single brief exposure to social stress in the establishment of a dominant-subordinate relationship results in a rapid decrease in the number of new cells produced in the dentate gyrus of subordinate tree shrews compared with those not exposed to a stressful experience (Gould et al 1997). Likewise, studies of marmosets using a resident intruder paradigm, a model of psychosocial stress similar to the dominant-subordinate paradigm used with tree shrews, have yielded similar results. In this paradigm, an adult male marmoset is introduced into the home cage of another male. Immediately after being placed in the cage, the intruder exhibits a stress response characterized by increased circulating corticosteroid and epinephrine levels, elevated mean arterial blood pressure, and dramatically increased heart rate. This experience rapidly suppresses cell proliferation in the dentate gyrus of intruder marmosets compared with naive controls (Gould et al 1998).

Repeated stress has been shown to produce prolonged suppression of cell proliferation in the dentate gyrus of adult tree shrews. It has been demonstrated that 28 days of exposure to a dominant animal for 1 hour each day results in a chronic increase in cortisol levels in adult tree shrews (Fuchs et al 1995). Exposure to chronic stress using this paradigm results in a decrease in new cell production in the dentate gyrus, which is associated with a decrease in the total granule cell layer volume (Fuchs et al 1997). It is likely that chronic suppression of granule cell production is partially responsible for the observed changes in granule cell layer volume; however, a direct causal relationship between the prolonged suppression of granule neuron production and decreases in the volume of the granule cell layer has yet to be established. It should be emphasized here that stress has a variety of effects on the hippocampus, including altering the structure of CA3 pyramidal cell dendrites (Fuchs et al 1995; Watanabe et al 1992). These types of stress-induced structural changes are likely to contribute to changes in hippocampal function as well.

Although well characterized in males, stress-induced changes in the production of granule neurons have not been investigated in females. A recent study has reported a sex difference favoring females in the production of new cells in the dentate gyrus of adult rats (Tanapat et al 1999). Moreover, female rats exhibit naturally occurring fluctuations in the numbers of new cells that are produced across the estrous cycle with maximal cell proliferation occurring during proestrus, the stage when estrogen levels are highest. Experimental manipulations in the levels of ovarian hormones add further support to the view that estrogen stimulates cell proliferation in adulthood (Tanapat et al 1999). Because females produce more new granule cells than males and yet have higher levels of circulating glucocorticoids (Handa et al 1994), it is likely that sex

differences exist in the mechanisms that regulate granule neuron production.

Functional Implications of Stress-Induced Changes in Postnatal Granule Neuron Production

Although stress has been shown to decrease the production of granule neurons in the developing dentate gyrus, the functional implications of this effect are not known. Nonetheless, the suppression of granule cell production during a time when the majority of granule neurons are produced is likely to have a significant effect on the structure of the adult hippocampal formation. This raises the possibility that stressful experiences during development is capable of exerting a long-term effect on hippocampal function by directly altering the structure of this brain region. The hippocampal formation has been implicated in learning and memory (McNaughton et al 1989; Squire and Zola 1998; Whishaw 1987). More specifically, the hippocampal formation is thought to be required for the acquisition of associations between temporally or spatially discontiguous events (Wallenstein et al 1998). Additionally, it has been suggested that the hippocampal formation is necessary for the acquisition of declarative memory (Squire and Zola 1998). These assertions raise the possibility that decreases in the production of granule neurons during development may have a negative impact on learning and memory in adulthood. Although there is some evidence to support the idea that stressful experience during development is correlated with impaired cognitive function (Siegel et al 1993), an involvement of stress-induced changes in granule neuron production has not yet been investigated.

Although the exact functional significance of late-generated neurons is not known, several lines of evidence suggest that these new cells play an important role in learning. In a recent study, it has been demonstrated that training in a task that requires the hippocampal formation for acquisition results in an increase in the number of adult-generated granule cells (Gould et al 1999). In untrained laboratory animals, the majority of adult-generated cells degenerate within 2 weeks of production (Cameron et al 1993b); however, training on either of two hippocampal-dependent tasks, place learning in a Morris water maze or trace eye-blink conditioning, results in the rescue of a significant proportion of these cells (Gould et al 1999). In the Morris water-maze task, rats utilize extramaze spatial cues to locate a hidden platform in a pool of water. Previous studies have demonstrated that lesioning of the hippocampal formation prevents the acquisition of this task (Morris et al 1982). With as little as 4 days of training, rats that learned the location of the hidden platform demonstrated a greater than twofold increase in the survival of adult-generated cells compared with animals that remained in a pool of water in the absence of a platform and compared with naive controls. Similar results have been observed using trace eye-blink conditioning. In this paradigm, rats learn to associate an unconditioned stimulus (US; shock to the eyelid) and a conditioned stimulus (CS; white noise) that are temporally separated. Consistent with the results obtained using the Morris water maze, as little as 4 days of training was sufficient to result in a greater than twofold increase in the number of adult-generated granule neurons compared with rats that were presented with the US and CS in an unpaired manner.

Taken together with the observation that stress suppresses the production of granule neurons, the finding that learning enhances the number of granule neurons suggests that stress-induced changes in neurogenesis may affect certain types of learning. It is important to note, however, that functional changes are not likely to be immediately evident. New cells require time to differentiate and become incorporated into functional circuitry. Thus, it is the period following stress-induced changes in cell proliferation that is most likely to be functionally relevant. Nonetheless, it recently has been demonstrated that adult-generated cells in the dentate gyrus extend axons into the CA3 region of the hippocampal formation as early as 4–10 days following division (Hastings and Gould 1999). Therefore, the impact of changes in cell production, although not immediately evident, may be functionally significant as early as 4 days later. Additionally, it is important to note that functional changes attributable to acute changes in cell production are not likely to be observed. For this reason, the impact of stress-induced changes in neuron production are most likely to be of interest when considering conditions of chronic stress because the effects are likely to be additive. Thus, although previous studies have demonstrated enhancements in learning as a result of conditions of acute stress (Wood and Shors 1998), mechanisms that underlie these effects are likely to involve processes other than changes in neuron production, such as changes in synaptic efficacy.

Several studies have demonstrated that chronic stress affects learning. Rats that were exposed to 21 days of restraint stress for 6 hours each day demonstrated impaired performance on the eight-arm radial maze (Luine et al 1994). The stressed rats made their first mistake earlier and exhibited fewer correct responses compared with unstressed control animals (Luine et al 1994). In addition, later studies have demonstrated that a stress-induced impairment of spatial learning on different tasks can be observed with both a shorter and longer duration of stress. For example, 8 days of psychosocial stress results in impaired performance on the hole board spatial discrimination task (Krugers et al 1997), and exposure to 6 months of psychosocial stress results in

impaired performance on the Morris water maze (Bodnoff et al 1995). The stress-induced impairment observed is not permanent; rats that were tested on the radial-arm maze 18 days following the termination of stress performed comparably to control rats (Luine et al 1994). This observation is consistent with a possible involvement of adult-generated cells in hippocampal function. If adult-generated cells are indeed necessary for normal performance on this task, an impairment may persist only as long as the production of these cells is altered. Once the stress-induced decrease in the number of new cells is no longer present, normal levels of performance should be restored. Stress-induced impairments during the early postnatal period, when the granule cell layer is forming, may have lasting effects, however. Alternatively, experience-dependent changes during development, when granule cell genesis is maximal, may be more readily compensated for by subsequent cell production. These possibilities have not yet been explored.

Several lines of evidence suggest that the observed impairment in hippocampal-dependent learning associated with conditions of chronic stress is likely to be mediated by elevated glucocorticoids. First, aging, a condition that is associated with chronic elevations in cortisol levels, is also associated with impairment of cognitive function and particularly those functions that are associated with the hippocampal formation (McEwen et al 1997). Second, electrophysiological abnormalities and deficits in learning and memory have been linked to changes in dentate gyrus following adrenal steroid treatment (Pavlides et al 1993). Third, it has been shown that long-term treatment with corticosterone is associated with impaired performance on the Morris water maze in rats (Bodnoff et al 1995; Endo et al 1996). Conversely, continuous blockade of brain glucocorticoid receptors facilitates spatial learning in the Morris water maze (Oitzl et al 1998). Collectively, these findings suggest that stress-induced decreases in the production of neurons may result in an impairment of hippocampal-dependent learning; however, a direct relationship between chronic stress-induced decreases in granule neuron production and learning has not been investigated.

Conclusion

Granule neurons in the dentate gyrus are produced during postnatal development and throughout adulthood. Stressful experience has been shown to suppress this process via mechanisms that are likely to involve adrenal steroids acting through a NMDA-receptor-mediated pathway. At present, the functional implications of stress-induced decreases in granule neuron production are not known. Nonetheless, decreases in granule neuron production during development are likely to alter the structure and function of the adult hippocampal formation. In addition, recent evidence indicates that granule neurons generated during adulthood are affected by, and potentially involved in, hippocampal-dependent learning. Previous studies have demonstrated that chronic stress suppresses the production of granule neurons during adulthood and also results in impaired performance on hippocampal-dependent tasks. Collectively, these findings suggest the possibility that stressful experience may impair hippocampal function via the suppression of granule cell production. In general, the degree to which the structure of the adult brain can be altered by experience is limited by the fact that neurons in most brain regions are produced during a discrete period of early embryonic development. Thus, the postnatal production of neurons in the dentate gyrus presents an unusual situation in which the experience of an organism may have dramatic and potentially long-lasting effects on the hippocampal structure and function.

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