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Stress and Adult Neurogenesis

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ABSTRACT: Stress hormones have potent growth-inhibiting effects on a variety of peripheral tissues. Consistent with this general function, stress has been shown to inhibit cell proliferation and, ultimately, neurogenesis in the hippocampus. This effect appears to be common across mammalian species, life stages, and most types of stressors. Although some evidence points to a role for glucocorticoids in mediating this effect, contradictory data exist. This review considers the growing literature on this subject with specific emphasis on paradoxical findings and the role of glucocorticoids in modulating adult neurogenesis.

KEY WORDS: dentate gyrus; neurogenesis; stress; glucocorticoids; hippocampus

INTRODUCTION

A major component of the "fight or flight" reaction involves mobilizing energy stores to deal with an imminent crisis (Selye, 1976). Maximizing available energy for the purposes of successfully escaping immediate danger, however, often comes at the expense of less vital functions. This is clearly an adaptive response designed to shunt energy normally spent in anticipation of the future, e.g., to support growth, toward processes that increase the chance of survival. In this regard, the catabolic and growth-inhibiting effects of stress hormones have long been recognized. Glucocorticoids suppress cell proliferation and promote cell death in numerous cell types, including thymocytes (McConkey et al., 1989), myocytes (te Pas et al., 2000), and osteoblasts (Chen, 2004). So it is perhaps not surprising that one of the actions of stress on the adult brain is to slow the production of new neurons. This review considers the burgeoning literature on the subject of stress and neurogenesis with a specific emphasis on unanswered questions, paradoxical findings, and functional consequences related to this phenomenon.

STRESS AND NEUROGENESIS: AN OVERVIEW

Numerous studies have reported that stress decreases the proliferation of progenitor cells in the dentate gyrus (DG) of the hippocampus. There is substantial evidence supporting the view that this phenomenon is a general one that is not dependent on species, stressor, or life stage. Stress-induced suppression of cell proliferation in the DG of adult animals has been reported in at least four different species (mouse, rat, tree shrew, and marmoset), suggesting that it may be a general character of mammals. Likewise, the effect appears to generalize across stressors; that is, similar results have been obtained with a variety of paradigms, including subordination stress (Gould et al., 1997), resident-intruder stress (Gould et al., 1998), footshock (Malberg and Duman, 2003; Vollmayr et al., 2003), restraint stress (Pham et al., 2003; Bain et al., 2004), isolation (Dong et al., 2004), cold immobilization (Heine et al., 2004b), cold swim (Lee et al., 2002; Heine et al., 2004b), and predator odor (Tanapat et al., 2001; Falconer and Galea, 2003; Mirescu et al., 2004). In general, schedules of stress exposure do not seem to be a critical determinant of this effect as both acute and chronic stress decrease cell proliferation. Finally, stress-induced inhibition of cell proliferation in the DG appears to occur throughout most of postnatal life, with similar results reported for the early postnatal period, young adulthood, and in the middle aged (Tanapat et al., 2001, 1998; Simon et al., 2005). There are no studies yet examining the influence of stress on neurogenesis in the aged animal. However, since aging is associated with a steep decline in baseline adult neurogenesis (Seki and Arai, 1995; Kuhn et al., 1996; Cameron and McKay, 1999), it may be impossible to detect further decreases with stress in the aged.

Some evidence suggests that the effect of stress on cell proliferation may be dependent on the sex of the animal; consistent inhibitory effects on this measure have been reported in males with either no effect or stimulatory effects on proliferating cells seen in females (Falconer and Galea, 2003; Westenbroek et al., 2004). However, since detailed time course studies have not been carried out in either males or females, the possibility that females do exhibit a stress-induced inhibition of cell proliferation, but at a different time following stress, cannot be ruled out.

Studies have also examined the influence of stress on the production of new neurons and these results are more complicated than studies examining cell proliferation. Several reports have shown that the effects of stress on cell proliferation in the DG result in a suppression of new neuron production (Czeh et al., 2002; Pham et al., 2003; Westenbroek et al., 2004). However, other studies have demonstrated that the influence of stress on adult neurogenesis is very short-lived, with diminished cell proliferation resulting in decreased immature neuron production followed by a period of enhanced cell survival, as the ultimate num-

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ber of new mature neurons appears unchanged (Tanapat et al., 2001; Malberg and Duman, 2003). The reasons for this inconsistency remain unknown.

CHARACTERIZATION OF THE PHENOMENON—QUESTIONS REMAINING

Psychological Factors

Despite the fact that stress-induced decreases in the numbers of proliferating cells, immature neurons and, in some instances, new mature neurons have been well-documented, some basic questions related to this phenomenon remain. First, although stress effects on cell production have been reported with a wide range of manipulations, ranging from physical stressors (e.g., foot shock) to psychological stressors (e.g., subordination stress), it remains unknown whether or not psychological variables alter the response of neurogenesis to stress. Since the initial work of Weiss (1970, 1972), we have known that psychological variables can determine the impact otherwise identical stressors have on the organism. Predictability and controllability are two variables that are known to lessen the negative consequences of stress on the brain and body (Tsuda and Tanaka, 1985; Shors et al., 1989; Araujo et al., 2003). Most published reports of stress effects on cell production in the DG have employed stressors that are uncontrollable and unpredictable. However, recent work suggests that controllability may be a major factor in determining the response of neurogenesis to stress; active avoidance learning, which is stressful but nonetheless controllable, appears to have no effect on cell proliferation in the DG (Van der Borght et al., 2005). This is consistent with preliminary studies suggesting that controllability may be an important protector against stress-induced decreases in adult neurogenesis (Shors et al., 2005). Studying the psychological variables that modulate this response may provide clues for determining the mechanisms that underlie stress-induced changes in neurogenesis. In some cases, manipulating psychological variables does not induce changes in hypothalamic pituitary adrenal (HPA) axis responsivity (Maier et al., 1986; Prince and Anisman, 1990; Kant et al., 1992), suggesting a possible dissociation between hormonal responses and neurogenesis.

Manipulating psychological variables in stress paradigms may result in the emergence of individual differences in stress effects on neurogenesis. However, in this regard, learned helplessness paradigms have been examined for differential actions on neurogenesis. For mostly unknown reasons, a certain proportion of rats will develop "learned helplessness" in response to chronic, uncontrollable stress. Despite differential behavioral responses to this experience, available evidence suggests that the effect on adult neurogenesis is the same in the rats that developed the syndrome and those that did not (Vollmayr et al., 2003). Although more work is needed in this area, this study suggests a potential dissociation between stress effects on adult neurogenesis and the emergence of helplessness.

Permanence vs. Resilience

Another unresolved issue is whether or not the effects of stress on adult neurogenesis are permanent. Studies examining the long term consequences of stress during development have revealed pronounced lasting effects on cell proliferation. Restraint stress of pregnant rats and acoustic startle stress of pregnant macaques produce a lasting suppression of cell proliferation in the DG of the offspring (Lemaire et al., 2000; Coe et al., 2003). In rats, this suppression extends into adulthood (Lemaire et al., 2000). Likewise, maternal separation during the early postnatal period inhibits cell proliferation and the production of immature neurons in the DG of adult offspring (Mirescu et al., 2004). Similarly, rats subjected to chronic or intense uncontrollable stress in adulthood also exhibit prolonged inhibition of cell proliferation in the DG (Malberg and Duman, 2003; Heine et al., 2004b). By contrast, rats subjected to acute stress in adulthood appear to exhibit a recovery of baseline cell proliferation by the following day (Heine et al., 2004b). The extent to which such resiliency is dependent on the age of the animal, as well as the intensity and duration of the stressor, remains to be determined.

GLUCOCORTICOID INVOLVEMENT IN STRESS-INDUCED INHIBITION OF NEUROGENESIS

Although the cascade of events leading to a reduction in adult neurogenesis in the DG following stress is far from understood, substantial evidence suggests that stress hormones play an important role. Aside from the fact that the hippocampus is richly endowed with adrenal steroid receptors and glucocorticoid manipulations have many structural and functional effects on this brain region (McEwen, 1999), a major reason to suspect these hormones as chief mediators of the neurogenesis effect is that glucocorticoids themselves regulate adult neurogenesis. Removal of circulating adrenal steroids by adrenalectomy increases cell proliferation and adult neurogenesis in young adult and aged rodents (Gould et al., 1992; Cameron and Gould, 1994; Cameron and McKay, 1999) as do other methods of inhibiting HPA axis activity, such as blockade of CRF-1 and V1b receptors (Alonso et al., 2004). By contrast, increased exogenous corticosterone suppresses this process both during the early postnatal period and in adulthood (Gould et al., 1991; Cameron and Gould, 1994). The similarities between these findings and those observed with stress point to glucocorticoids as the primary mediator of stress effects. Direct support for this comes from studies showing that adrenalectomy with low dose corticosterone replacement in the drinking water, which prevents the stress-induced rise in corticosterone while maintaining its diurnal rhythm, eliminates the stress effect on neurogenesis in the adult DG (Tanapat et al., 2001; Mirescu et al., 2004). Collectively, this evidence suggests that stress inhibits cell proliferation, and new neuron formation, via increasing glucocorticoids.

DIRECT AND INDIRECT EFFECTS OF GLUCOCORTICOIDS

Within the brain, the actions of glucocorticoids are mediated by two types of adrenal steroid receptors (Reul and de Kloet, 1985). Both the high-affinity mineralocorticoid receptor (MR) and the low-affinity glucocorticoid receptor (GR) exist in the hippocampus. Almost all MR binding sites in the hippocampus are occupied under baseline, unstressed conditions, indicating that these receptors are not primarily involved in responding to stress-induced increases in glucocorticoids. By contrast, fewer GR binding sites are activated under baseline conditions such that significant changes in binding of this receptor can be observed following stress. Thus, based on the properties of this receptor, GRs are most likely responsible for the effects of glucocorticoids on neurogenesis. Some evidence directly suggests that the GR agonist dexamethasone inhibits neurogenesis both in vivo and in vitro (Kim et al., 2004). Furthermore, pharmacological blockade of this receptor has a restorative effect on the suppression of cell proliferation produced by elevated corticosterone (Wong and Herbert, 2005), demonstrating the specific involvement of GRs. Although only 10–20% of progenitor cells in the DG appear to express MR or GR (Cameron et al., 1993; Garcia et al., 2004), the possibility remains that the effects of stress on neurogenesis may be mediated directly on this subpopulation of progenitors.

Stress-induced decreases in the numbers of proliferating cells could be the result of either a loss of progenitor cells or slowing/arrest of the cell cycle. However, the speed with which stress-induced reductions in proliferating cells can be observed (detectable as early as a few hours after stress) argues against the former possibility. Indeed, the recent observation that chronic stress not only reduces the numbers of proliferating cells in the subgranular zone but concomitantly elevates levels of p27Kip1, an endogenous cell cycle inhibitor, specifically suggests that stress may prevent progenitors from cell cycle reentry (Heine et al., 2004a). At least in mouse epithelial cell lines, it appears that the glucocorticoid-induced increase of p27Kip1 is dependent upon GR activation (Jiang et al., 2002), suggesting that a similar effect might be mediated directly through actions on some of the progenitor cells expressing GR in the DG.

Alternatively or in addition to the direct involvement of GR signaling, stress-induced reductions in cell proliferation may occur through indirect mechanisms and more generally impact the entire population of progenitor cells in the DG. Stress increases glutamate release in the hippocampus (Lowry et al., 1993; Abraham et al., 1998), and several lines of evidence suggest that enhanced excitatory neurotransmission reduces cell proliferation. In both developing and adult animals, NMDA receptor activation reduces the number of new cells in the DG, while blockade of NMDA receptors or lesion of the entorhinal cortex, which provides the major excitatory input to the DG, has the opposite effect on cell proliferation (Cameron et al., 1995; Nacher et al., 2003; Okuyama et al., 2004). Moreover, blocking NMDA receptors prevents exogenous corticosterone from inhibiting cell proliferation (Cameron et al., 1998). While a detailed understanding of the events leading to decreased cell proliferation following stress remains unknown, it is likely that in some cases, stress-induced increases in glucocorticoids stimulate glutamate release which exerts negative effects on cell proliferation. The extent to which such a mechanism operates in concert with direct inhibitory actions of glucocorticoids on a subpopulation of progenitor cells is another open question.

SOME PARADOXICAL FINDINGS

There are some interesting counterexamples to the claim that glucocorticoids inhibit neurogenesis. These raise issues of the complex nature of certain experiences and the multiple factors regulating neurogenesis. In some studies, living in an enriched environment (Benaroya-Milshtein et al., 2004; Moncek et al., 2004) and training on learning paradigms (Leuner et al., 2004) appear to increase circulating glucocorticoid levels. Yet, both enriched environment living and learning have been associated with enhanced neurogenesis, typically by enhancing survival of new cells (Kempermann et al., 1997; Nilsson et al., 1999; see Leuner et al., current issue). These results may seem contradictory since glucocorticoid elevations under many other conditions are associated with an inhibition of cell proliferation and neurogenesis. However, these experiences, i.e., environmental complexity and learning, undeniably impart a wide range of changes to the organism, above and beyond the effects on glucocorticoids. Thus, the positive influences of these experiences on adult neurogenesis must, in some way, override the negative effect of elevated glucocorticoids.

A striking example of an unexpected relationship between circulating glucocorticoid levels and cell proliferation also occurs with physical activity. Running is a well-known activator of the HPA axis (Droste et al., 2003) that also increases adult neurogenesis (van Praag et al., 1999a,b; Fabel et al., 2003; Farmer et al., 2004). Previously sedentary animals experience elevated glucocorticoid levels shortly after they begin running and no adaptation of this response occurs as animals become more physically fit. It should be noted that increases in glucocorticoids with physical activity occur only during certain times of day (Droste et al., 2003), and so the negative effects on neurogenesis may not be as profound as those observed with exposure to negative stressors. An interesting contradiction to the generally positive effects of running on adult neurogenesis exists with studies on spontaneously hypertensive rats. These animals that run much greater distances than other rat strains exhibit greater activation of the HPA axis and suppressed adult neurogenesis when given access to a running wheel (Naylor et al., 2005), suggesting that running-induced factors which stimulate neurogenesis are only effective when HPA axis activation is minimal.

In addition to these studies reporting increased neurogenesis under conditions that simultaneously elevate glucocorticoids, some experiments have revealed no change in cell proliferation in the DG despite elevated glucocorticoids. Certain stress paradigms, such as restraint stress (Pham et al., 2003) and active

avoidance shock training (Van der Borght et al., 2005), have been shown to elevate corticosterone levels and have no measurable effect on cell proliferation. In the case of restraint stress, inhibition of cell proliferation and neurogenesis occurs when the stress is chronic and appears to be disconnected with glucocorticoid levels (Pham et al., 2003). The reasons for these discrepancies remain unknown, but as in the case with running, the degree of activation of the HPA axis may be the critical factor.

Another set of studies have reported no apparent connection between glucocorticoid levels and suppressed neurogenesis. These studies have demonstrated persistent inhibition of neurogenesis despite restoration of normal levels of glucocorticoids. For instance, stressors occurring early in life have been shown to decrease cell proliferation (Lemaire et al., 2000; Mirescu et al., 2004) not only at the time of stress (Tanapat et al., 1998; Zhang et al., 2002), but also into adulthood when basal levels of adrenal steroids appear to be normal (Mirescu et al., 2004). Similarly, Malberg and Duman (2003) have reported reduced cell proliferation at the time of stress (when plasma corticosterone is indeed elevated); however, the reduction in cell proliferation persisted well after the baseline levels of corticosterone had been restored. These findings suggest that while glucocorticoids may be involved in the initial suppression of cell proliferation, they are no longer necessary for maintaining prolonged responses. Alternatively, it is possible that glucocorticoids continue to be involved in reducing cell proliferation but that this influence is not detectable by merely examining total peripheral levels of glucocorticoids. Support for this view comes from the observation that diminished cell proliferation in maternally separated rats can be restored to normal by reducing levels of circulating glucocorticoids (Mirescu et al., 2004). This raises the question of whether additional factors can modulate adult neurogenesis through glucocorticoids in the absence of measurable differences in circulating glucocorticoids.

ADDITIONAL MECHANISMS AFFECTING GLUCOCORTICOID ACTION

There are several other ways stress may modulate the availability of glucocorticoids to the hippocampus. For instance, alterations in levels of corticosteroid binding globulin (CBG), a protein known to bind glucocorticoids, may affect the amount of free glucocorticoids available to enter the brain and alter cell proliferation. Studies of maternal separation and tailshock in adulthood have found decreased CBG levels, with no change in total corticosterone level, in the blood (Fleshner et al., 1995; Viau et al., 1996; Deak et al., 1999; Weaver et al., 2000). Thus, certain types of stress (developmental or repeated inescapable) may render animals temporarily more sensitive to glucocorticoids by increasing the ratio of free to bound corticosterone while maintaining the overall levels of this hormone. This mechanism may also contribute to the contradictory findings of enhanced neurogenesis under conditions of elevated glucocorticoids, since some evidence suggests that running is also associated with elevated levels of CBG (Droste et al., 2003).

Glucocorticoid action on the brain depends not only on whether free hormone is available to cross the blood brain barrier, but whether steroid transporters permit this to occur. Although no studies have yet reported stress-induced modulation of steroid transport, one type of glucocorticoid transporter, multidrug resistance glycoprotein (MDR-PGP), appears to be concentrated in endothelial cells of the hippocampus (Kwan et al., 2003). Additionally factors within target cells themselves can also modulate local glucocorticoid levels within the hippocampus. The enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD) is known to exhibit bidirectional regulation of corticosterone activity. While the 11β-HSD type 2 isozyme converts corticosterone to inactive cortisone, the type 1 isozyme acts as a reductase, regenerating active corticosterone from cortisone (Holmes et al., 2003). In the hippocampus, 11β-HSD reductase function appears to predominate (Yau et al., 2001; Ajilore and Sapolsky, 1999), thereby amplifying local hormone levels and action. Although the potential relationship between local control over corticosterone levels and neurogenesis remains unknown, stress has been shown to modulate levels of this enzyme within the hippocampus (Jamieson et al., 1997), suggesting that this is an important mechanism to consider. In addition to the aforementioned possibilities, the larger literature on this subject (reviewed in Sapolsky et al., 2000) should be considered before glucocorticoid involvement is ruled out as a causal factor in cell proliferation changes on the basis of failure to find correlations between adult neurogenesis and blood levels of corticosterone.

ARE THERE FUNCTIONAL CONSEQUENCES OF STRESS-INDUCED SUPPRESSION OF NEUROGENESIS?

The adaptive significance of stress-induced inhibition of adult neurogenesis seems obvious when considered in the larger context of stress effects on many other tissues. Growth inhibition is probably a reasonable compromise during stress, when energy must be mobilized to insure survival of the organism. However, the question of whether or not repeated bouts of stress-induced inhibition of neurogenesis have functional consequences, whether positive or negative, remains unanswered. Multiple studies have linked adult neurogenesis with functions of the hippocampus, including learning and memory (see Leuner et al., this issue for review), as well as with the development of psychopathology and recovery from brain damage. These studies present the possibility that stress-induced changes in neurogenesis may have cumulative effects that ultimately alter one or more of these processes. Indeed, stress has been shown to influence learning and memory as well as to precipitate and exacerbate mood disorders (McEwen, 2005; Nemeroff and Vale, 2005). It is tempting to speculate that stress alters hippocampal function by acting solely on adult neurogenesis. However, stress influences a vast number of cellular processes, including the maintenance of dendritic architecture, synaptic plasticity, neurotransmission, and growth factor levels, not just

within the hippocampus but throughout the brain (McEwen, 1999). The more likely scenario is that, if neurogenesis inhibition contributes to stress effects on brain function, it does so in concert with multiple other mechanisms.

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