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Hippocampal Neurogenesis: Opposing Effects of Stress and Antidepressant Treatment

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ABSTRACT: The hippocampus is one of several limbic brain structures implicated in the pathophysiology and treatment of mood disorders. Preclinical and clinical studies demonstrate that stress and depression lead to reductions of the total volume of this structure and atrophy and loss of neurons in the adult hippocampus. One of the cellular mechanisms that could account for alterations of hippocampal structure as well as function is the regulation of adult neurogenesis. Stress exerts a profound effect on neurogenesis, leading to a rapid and prolonged decrease in the rate of cell proliferation in the adult hippocampus. In contrast, chronic antidepressant treatment up-regulates hippocampal neurogenesis, and could thereby block or reverse the atrophy and damage caused by stress. Recent studies also demonstrate that neurogenesis is required for the actions of antidepressants in behavioral models of depression. This review discusses the literature that has lead to a neurogenic hypothesis of depression and antidepressant action, as well as the molecular and cellular mechanisms that underlie the regulation of adult neurogenesis by stress and antidepressant treatment. © 2006 Wiley-Liss, Inc.

KEY WORDS: depression; proliferation; granule cells; VEGF; BDNF

INTRODUCTION

Depression is a pervasive and debilitating illness that affects as many as one in five Americans at some point in their lives (Kessler et al., 1994). The symptoms of depression fall into three primary categories, including changes in mood (e.g., sadness, anhedonia, irritability), basic drives (e.g., sleep, eating), and cognitive disturbances (e.g., ruminations, guilt, indecisiveness, persistent thoughts of suicide). This constellation of diverse symptoms indicates that a number of limbic brain structures underlie depression (Drevets, 2001). Although the identification of exact neural substrates is still under investigation, the hippocampus has received a great deal of attention. This is due to several related factors. First, the hippocampus expresses high levels of receptors for the stress-responsive adrenal-glucocorticoids, and an elevated hypothalamic–pituitary–adrenal (HPA) axis is one of the hallmark neuroendocrine markers of depression (Holsboer and Barden, 1996; Gold and Chrousos, 2002). Second, the hippocampus plays a significant role in negative feedback regulation of the HPA axis, which controls glucocorticoid release and is often disinhibited in depressed subjects (Young et al., 1991; Sapolsky, 2001). Third, chronic stress or elevated glucocorticoids can lead to atrophy or loss of hippocampal neurons, which in turn can lead to further loss of the feedback inhibition of the HPA axis provided by this structure (Young et al., 1991; McEwen, 1999; Sapolsky, 2001). Fourth, the hippocampus shares anatomical connections with the amygdala and prefrontal cortex, two highly studied brain areas that have been implicated in mood and cognition (Drevets, 2001).

This combination of factors has focused research on the hippocampus as one of several limbic brain structures involved in the etiology and treatment of depression, although it is important to acknowledge that it cannot directly account for all of the symptoms of mood disorders. In addition to the loss of feedback inhibition of the HPA axis, dysfunction of the hippocampus could also directly contribute to the cognitive deficits observed in depression. The hippocampus could also contribute to increased anxiety and indirectly influence mood and cognition via connections with the amygdala and the prefrontal cortex. Finally, recent studies demonstrate that hippocampus also controls the activity and function of mesolimbic dopamine neurons in a way that could influence reward and pleasure, and disruption of this pathway could contribute to anhedonia, another hallmark symptom of depression (Lisman and Grace, 2005). On the basis of these observations, the hippocampus can be considered as one of the several limbic structures that can either directly or indirectly contribute to several of the core symptoms of depression.

Although the molecular and cellular mechanisms underlying depression and the actions of antidepressant treatment have not been fully elucidated, studies over the past 10 years have contributed to a neurotrophic and neurogenic hypothesis, with much of the evidence based on studies of the hippocampus (Duman, 2004a,b). This hypothesis is based on reports demonstrating that stress decreases neurotrophic factor expression and neurogenesis in the adult hippocampus, effects that could contribute to the atrophy of hippocampus observed in depressed patients. In contrast, antidepressant treatments can increase neurotrophic factor expression and adult-hippocampal neurogenesis and could thereby reverse or block the effects of stress on hippocampal atrophy. This review will provide a brief overview of the basic and clinical studies demonstrating anatomical evidence for hippocampus, as well

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as evidence of atrophy of hippocampus in mood disorders. A more complete review will be provided on the role of hippocampal neurogenesis in stress, depression, and the actions of antidepressant treatments.

HIPPOCAMPAL VOLUME IS DECREASED IN DEPRESSION

Clinical studies have demonstrated that subjects with depression have reduced hippocampal volume, as well as atrophy of other limbic brain regions. This section provides a brief review of the brain imaging literature on this subject, and postmortem studies of the cellular changes that could underlie alterations of hippocampal size.

Brain Imaging of Depressed Subjects

The hippocampus, prefrontal cortex, and amygdala are three regions of critical interest in studies of the underlying pathophysiology of depression (Drevets, 2001). Numerous volumetric and functional brain imaging studies have examined these regions in depressed patients compared to healthy controls. Although it is not yet clear where the initial insult occurs, there is strong evidence demonstrating that the volume of these regions is altered in depressed patients.

There are numerous reports demonstrating that the volume of the hippocampus is decreased in depressed subjects. (Sheline et al., 1996; Shah et al., 1998; Sheline et al., 1999; Bremner et al., 2000; Mervaala et al., 2000; Steffens et al., 2000; Frodl et al., 2002; MacQueen et al., 2003; Saarelainen et al., 2003; Sheline et al., 2003; Vermetten et al., 2003). There are a few negative studies, and this could be due to variability in patient inclusion and definition of the hippocampal region analyzed (Axelson et al., 1993; Vakali et al., 2000). Also, there are reports that antidepressant treatment can reverse or block hippocampal atrophy (Sheline et al., 2003; Vermetten et al., 2003). In addition to decreased hippocampal volume, reductions in the volume of the prefrontal cortex (Drevets et al., 1997; Ongur et al., 1998; Hirayasu et al., 1999; Rajkowska et al., 1999; Bremner et al., 2000; Rajkowska et al., 2001) and amygdala have been reported in depressed subjects (Hastings et al., 2004).

Postmortem Studies of Depressed Patients

To examine the underlying cellular alterations that could account for the atrophy of hippocampus, studies on postmortem tissues from depressed subjects are being conducted. One study has reported an increase in cell packing density in the hippocampus, an effect that could contribute to the decreased hippocampal volume in depressed subjects (Stockmeier et al., 2004). Consistent with the increase in packing density is the finding of a 30–35% increase in the density of neurons and glia in the pyramidal subfields and dentate gyrus (DG) of the hippocampus (Stockmeier et al., 2004). An earlier study did not find differences in hippocampal cell number in the hippocampus of depressed subjects, although discrete cell counts and morphometric analysis were not conducted (Muller et al., 2001). Another more recent study of the volumes of subcortical structures reported volume reductions in several areas, including hippocampus and amygdala (Bielau et al., 2005). In addition to the studies of hippocampus, there are several studies reporting a reduction in the number of glia and size of neurons in the prefrontal cortex of depressed subjects (see Duman, 2004a).

To address the functional consequences of these volumetric reductions, von Gunten and Ron (2004) have correlated the magnitude of right hippocampal volume reduction found in depressed patients with the degree of subjective memory impairment. They found a direct correlation; however, in the absence of a patient group with no memory impairments, the interpretation of this report is limited. It is not yet clear whether these volumetric reductions are causal or a consequence of depression. The impact of these morphometric data on brain function and depressive symptoms is an area that requires further investigation.

STRESS AND NEUROGENESIS IN THE ADULT HIPPOCAMPUS

Basic research has firmly established that neurogenesis persists in the adult mammalian brain (Kempermann et al., 1997; Eriksson et al., 1998; Gould et al., 1999; Gage, 2000;). The subgranular zone (SGZ) of the hippocampus is one of two major neurogenic zones where neural progenitors are found in the adult brain and continue to give rise to new neurons. Newborn cells proliferate in the SGZ, migrate into the granule cell layer (GCL), and mature into neurons and other cell types (Fig. 1). In addition, one of the most striking features of adult neurogenesis is that it is an extremely dynamic process that can be up- or down-regulated by a variety of endocrince, environmental, and pharmacological factors. This section reviews the use of stress as a model of depression and the influence of stress on neurogenesis in the adult hippocampus.

Stress Decreases Neurogenesis

Chronic stress is a risk factor for major depression in individuals with genetic vulnerability (Holsboer and Barden, 1996; Gold and Chrousos, 2002). In addition, repeated stress is often used as an animal model of depression in rodents because it induces symptoms of depression, including (1) anhedonia, measured by sucrose preference (Willner and Mitchell, 2002); (2) alterations in REM sleep (Moreau et al., 1995; Cheeta et al., 1997); (3) reduced sexual activity (D'Aquila et al., 1994; Brotto et al., 2001); (4) increased corticosterone levels (Gold and Chrousos, 2002); and (5) disturbed circadian rhythms (Stewart et al., 1990; Solberg et al., 1999). In this context, it is interesting to note that neurogenesis in the adult hippocampus is extremely sensitive to and markedly regulated by stress.

There are now numerous studies that consistently report that stress decreases the proliferation of new neurons in the SGZ of the hippocampus (Fig. 2). Adult neurogenesis is decreased by many different types of stressors, including predator odor (Galea

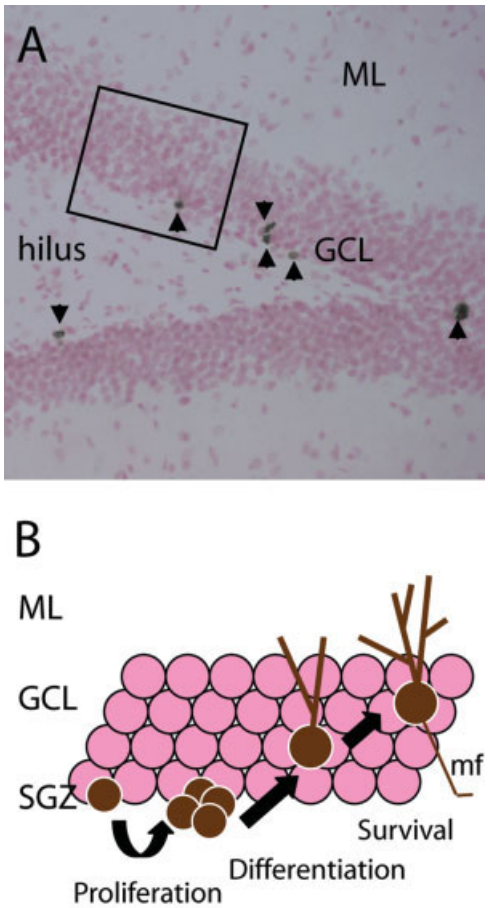

FIGURE 1. Neurogenesis in the adult hippocampus. A: depicts a typical image of newborn neurons in hippocampus of adult rat, visualized by immunohistochemistry for bromodeoxy uridine (BrdU), which is incorporated into the DNA of dividing cells, indicated with arrowheads. Putative neural stem cells are located in the SGZ of the hippocampus, localized at the border between the GCL and the hilus. The proliferating cells are irregular in shape and have very few or no processes. The diagram in (B) shows how many of the newborn cells (~80%) that are destined to become neurons migrate into the granule cell layer, mature, and take on characteristics of adult granule cells. Most notable is the extension of dendrites into the molecular layer and axons into the CA3 pyramidal cell layer via the mossy fiber pathway. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

et al., 2001), social stress (Czeh et al., 2001; Gould et al., 1997), acute and chronic restraint stress (Pham et al., 2003; Vollmayr et al., 2003; Rosenbrock et al., 2005), footshock stress (Malberg and Duman, 2003; Vollmayr et al., 2003), and chronic mild stress (Alonso et al., 2004). For a complete review of the literature on the regulation of neurogenesis by stress and antidepressants see Duman, 2004b. Inescapable stress also decreases neurogenesis with a time course that correlates with behavioral despair in the learned helplessness model of depression (Malberg and Duman, 2003). However, there is also a report of a dissociation between decreased neurogenesis and behavior in the learned helplessness model (Vollmayr et al., 2003). This indicates that neurogenesis does not underlie behavioral despair in this model, but could also reflect the limitations of learned helplessness model, a well as other behavioral models of depression that inadequately reproduce the time course and symptoms of depression.

Mechanisms for Down-Regulation of Neurogenesis by Stress

There are several possible mechanisms that could account for the effects of stress on adult neurogenesis. Stressful experiences stimulate the HPA axis, resulting in increased adrenal–glucocorticoid levels, one of the hallmark endocrine responses to stress. Glucocorticoid hormones act on two main subtypes of receptors in the brain: the mineralcorticoid receptor (MR) and the gluco-

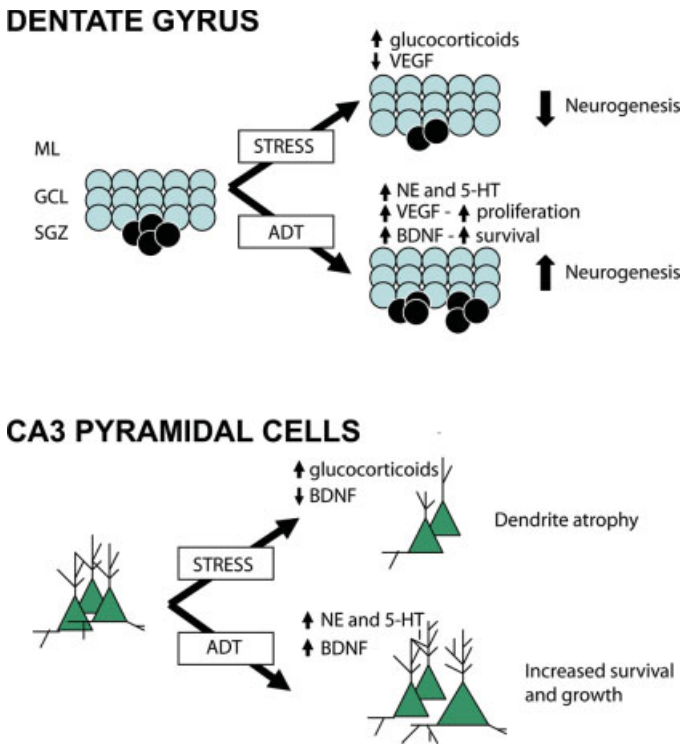

FIGURE 2. Molecular and cellular determinants underlying the opposing actions of stress and antidepressant treatment on hippocampal structure. Stress can have multiple effects depending on the subregion of the hippocampus examined. In the DG acute or chronic stress results in decreased neurogenesis or birth of new neurons. Neural progenitor cells are located in the SGZ, a region between the GCL and the hilus. Adrenal glucocorticoid, which are elevated by stress, also decreases adult neurogenesis. Stress also decreases the expression of BDNF and VEGF, effects that could contribute to decreased neurogenesis. In contrast, antidepressant treatment increases neurogenesis in the hippocampus, and the up-regulation of cell proliferation and survival is mediated by increased expression of VEGF and BDNF, respectively. In the CA3 pyramidal cell layer, repeated stress results in atrophy or remodeling of pyramidal neurons, decreasing the number and length of apical dendrites. Glucocorticoid administration causes a similar effect, and decreased expression of BDNF could contribute to pyramidal cell atrophy. Chronic antidepressant administration can reverse the atrophy of CA3 neurons. The effects of antidepressant treatment occur via acute regulation of 5-HT and NE and the regulation of intracellular signaling and gene expression. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

corticoid receptor (GR). Because of its lower affinity, the GR is activated primarily during periods of stress when circulating levels of glucocorticoids are relatively high. Upon activation, these receptors translocate to the nucleus of the cell where they trigger changes in gene expression, which have long-lasting effects on the structure and functioning of the cells. The enrichment of MR and GR in the hippocampus makes this structure particularly vulnerable to stress, and could underlie the down-regulation of neurogenesis. This possibility is supported by studies demonstrating that administration of corticosterone, the active adrenal glucorticoid in rodents, significantly decreases neurogenesis in the hippocampus (Fig. 2) (Gould et al., 1992; Cameron et al., 1998). Decreased neurogenesis in response to stress or corticosterone can be blocked by pretreatment with an NMDA receptor antagonist, demonstrating a role for enhanced glutamate transmission (Cameron and Gould, 1996).

Stress is also reported to decrease the expression of brain derived neurotrophic factor (BDNF) and it is possible that the reduced levels of this factor also contribute to the actions of stress (Duman, 2004a). In addition, a recent study has demonstrated that stress decreases levels of vascular endothelial growth factor (VEGF) in the hippocampus (Heine et al., 2005). VEGF was first shown to influence angiogenesis and proliferation of endothelial cells, but a role for VEGF in hippocampal neurogenesis has also been demonstrated, leading to a vascular niche hypothesis of depression (Palmer et al., 2000). Further studies will be required to determine the role of VEGF in the down-regulation of adult neurogenesis. Another factor that has received attention is interleukin-1β (IL-1β). Preliminary studies demonstrate that IL-1β, like stress, decreases neurogenesis and that blockade of IL-1β blocks the down-regulation of neurogenesis in response to stress (Koo and Duman, 2005).

In addition to decreased neurogenesis, stress influences the structure of mature neurons in the adult hippocampus. Stress, as well as corticosterone treatment, significantly reduces the length and number of branch points of CA3 pyramidal neurons in the hippocampus (Fig. 2) (Watanabe et al., 1992; Magarinos et al., 1996). Atrophy or restructuring of CA3 neurons could contribute to the reduction in hippocampal volume and increased packing density reported in depressed subjects. Further analysis of the fine structure of hippocampal neurons in the postmortem tissue of depressed subjects will be needed to examine this hypothesis. In addition to morphological alterations, stress and adrenal steroids regulate long-term potentiation (LTP) in rodent models (Foy et al., 1987; Shors et al., 1990), suggesting a significant impairment in hippocampal function after chronic stress exposure.

ANTIDEPRESSANTS AND NEUROGENESIS IN THE HIPPOCAMPUS

Previous hypotheses to explain the therapeutic action of antidepressants, as well as the theories of depression, were based on the acute action of these treatments to block the reuptake or metabolism of monoamines and thereby increase synaptic levels of these neurotransmitters. Despite an acute rise in the levels of the monoamines serotonin (5HT) and norepinephrine (NE), these treatments require chronic administration (weeks to months) before a therapeutic effect is observed. This has led to a cellular theory of depression (Duman et al., 1997) in which increases in 5HT/NE activate receptors to trigger intracellular signaling cascades that regulate gene transcription. These alterations in gene expression, including increased expression of neurotrophic factors, mediate long-lasting changes in cell morphology and functioning, which are thought to underlie the action of antidepressants in part by reversing stress-induced damage. Taken together, these findings support a role for increased hippocampal neurogenesis in the action of antidepressants.

Antidepressant Treatment Increases Adult Neurogenesis

In contrast to the effects of stress, antidepressant treatment increases adult neurogenesis (Fig. 2). Administration of one of the several different classes of antidepressants, including 5-HT or NE selective reuptake inhibitors, increases neurogenesis in adult hippocampus (Madsen et al., 2000; Malberg et al., 2000; Manev et al., 2001; Nakagawa et al., 2002; Santarelli et al., 2003). For a complete review of the literature on antidepressant regulation of neurogenesis see Duman, 2004b. The up-regulation of neurogenesis is dependent on chronic treatment, consistent with the time course for the therapeutic action of antidepressants (Malberg et al., 2000). The influence of antidepressants on the different aspects of neurogenesis, including proliferation, differentiation, and survival, has been examined. These studies demonstrate that chronic antidepressant administration increases the proliferation of neural progenitors in the SGZ (Malberg et al., 2000) and the survival of these newborn neurons (Nakagawa et al., 2002), but does not influence the ratio of neurons to glia (∼80:20) (Malberg et al., 2000). The pharmacological specificity of antidepressant regulation of adult neurogenesis has also been examined. Atypical antipsychotics, which are effective at remitting the symptoms of depression and enhance the effectiveness of SSRIs, increase proliferation as well (Kodama et al., 2004). However, classical antipsychotics, which do not effectively treat depression, have no effect on cell proliferation (Malberg et al., 2000; Halim et al., 2004; Wang et al., 2004), and drugs of abuse decrease neurogenesis (Eisch and Mandyam, 2004).

In addition to studying the effects of chemical antidepressants, the influence of electroconvulsive seizures (ECS), a model of electroconvulsive therapy (ECT), on proliferation and survival has been assessed. In humans, ECT is the most effective treatment for patients suffering from severe otherwise treatment resistant depression (UK ECT Group, 2003). Interestingly, ECS is a more potent stimulator of proliferation than chemical antidepressants (Madsen et al.,2000; Malberg et al., 2000), correlating with its relative therapeutic efficacy. ECS increases cell proliferation by ∼2.5-fold, compared to ∼1.5-fold for chemical antidepressants. These newborn cells integrate into the GCL and can be detected for at least three months after treatment cessation (Madsen et al., 2000). ECS increases the number of newborn neurons, glia, and endothelial cells in the GCL, but does not alter

the relative ratio of cell phenotype (Madsen et al., 2000; Wennstrom et al., 2003; Hellsten et al., 2004). Therefore, ECS and chemical antidepressants exert their neurogenic effect by increasing the rate of progenitor cell proliferation and by increasing the survival of newborn cells in the adult hippocampus.

It is worth mentioning that exercise, which is an effective antidepressant in humans (Blumenthal et al., 1999; Strawbridge et al., 2002) and in rodent models (Bjornebekk et al., 2005; Greenwood et al., 2005), is also a potent stimulator of proliferation in the adult hippocampus (van Praag et al., 1999). Other treatments known to have antidepressant efficacy, including estrogen and DHEA, also increase neurogenesis (Tanapat et al., 1999; Karishma and Herbert, 2002). Taken together, these data have identified neurogenesis as a target for the development of novel antidepressant medications (Duman, 2004a; Malberg and Schechter, 2005).

Antidepressant Treatment Blocks the Down-Regulation of Neurogenesis Caused by Stress

A neurotrophic hypothesis of depression suggests that the structural and morphological changes following chronic antidepressant treatment work to reverse the damaging effects caused by stress or depression. Using stress as a model of depression, several studies have found that antidepressant treatment can prevent and reverse decreased neurogenesis resulting from stressful experiences. Chronic antidepressant administration prevents the down-regulation of neurogenesis caused by psychosocial stress in the tree shrew (Czeh et al., 2001; van der Hart et al., 2002), chronic mild stress in mice (Alonso et al., 2004), or maternal separation in rats (Lee et al., 2000). In addition, chronic fluoxetine treatment blocks the reduction of neurogenesis caused by inescapable footshock in the rat, and there is corresponding reversal of behavioral despair in the learned helplessness model (Malberg and Duman, 2003). In addition, ECS increases cell proliferation after chronic corticosterone treatment (Hellsten et al., 2002). Taken together, these studies provide further support for a neurotrophic/neurogenic hypothesis of antidepressant action.

Functional Consequences of Antidepressant Regulation of Newborn Neurons

An important question that follows these morphological data is whether the newborn cells induced by antidepressant treatment integrate into the hippocampal cell network. In other words, are they functional neurons? In normal rodents, cells proliferate in the SGZ, migrate into the GCL, and make synaptic connections (Markakis and Gage, 1999). These newborn granule cells also display the same electrophysiological characteristics of neighboring mature cells (van Praag et al., 2002). Work is currently being conducted to determine the effects of antidepressants on synaptic structure and function of newborn, maturing neurons in the granule cell layer.

An even more critical question in the field is what is the behavioral impact of antidepressant-induced increases in hippocampal neuronal number? Drawing a direct, causal link between hippocampal neurogenesis and the therapeutic action of antidepressants has been an area of hot debate (Duman, 2004b; Henn and Vollmayr, 2004), and much of the data is correlative. The first attempt to address this question came in 2003, with a report by Santarelli and colleagues. They used low-doses of irradiation exposure to selectively kill dividing progenitor cells in the hippocampus. In animals receiving irradiation, the induction of neurogenesis by antidepressant treatment is blocked and the behavioral responses to two classes of antidepressants in mice was attenuated. Two different behavioral models that are responsive to chronic antidepressant treatment were tested: novelty-suppressed feeding and chronic mild stress. This was the first indication that neurogenesis is required for the behavioral actions of antidepressants and an important contribution to the field.

There are two important considerations for this study. The first is the use of irradiation to "turn-off" neurogenesis. Low doses were chosen for this study, as they have been shown to target and kill progenitors while sparing neighboring mature granule cells (Parent et al., 1999; Peissner et al., 1999). However, even at low doses, irradiation induces an inflammatory response that can have long lasting effects on the neurogenic microenvironment (Monje et al., 2003). This limitation was addressed by studies of a mutant mouse model, in which the induction of neurogenesis and the behavioral actions of antidepressants are both blocked by deletion of the 5-HT1A receptor, consistent with the irradiation results (Santarelli et al., 2003). Second, irradiation alone markedly decreased neurogenesis but did not influence baseline behavioral responses in novelty-suppressed feeding or chronic mild stress. This indicates that although induction of neurogenesis is required for an antidepressant response, reduction of the basal rates of neurogenesis do not result in a depressive-like phenotype in these animal models. This could result in part from limitations of the animal models. For example, novelty-suppressed feeding is an accepted test of anxiety (Bodnoff et al., 1988), and the reason that it was chosen, as well as the chronic mild stress paradigm, for the neurogenesis studies is because these models are responsive to chronic, not acute, antidepressant administration (Bodnoff et al., 1988). More traditional behavioral tests such as learned helplessness or the forced swim test are responsive to acute or subchronic administration of antidepressants (Cryan et al., 2002), and are not as suitable for studies of neurogenesis. It is possible that antidepressants influence behavior in these models by regulation of synaptic function of newborn, as well as mature neurons, a possibility supported by recent studies demonstrating antidepressant regulation of synaptic signaling proteins and spine formation in the hippocampus (Hajszan et al., 2005; Zinc et al., 2005).

MECHANISMS UNDERLYING THE NEUROGENIC ACTION OF ANTIDEPRESSANTS

A major question in the field, not just related to the actions of antidepressants but more generally to the field of neurogenesis is what underlies the neurogenic action of antidepressants, as well

as basal rates of neurogenesis? The answers have significant ramifications and could lead to novel strategies for inducing neurogenesis outside the major neurogenic zones for the treatment of a wide range of neurological and neurodegenerative disorders. Similarly, since neurogenesis is a target for antidepressants, elucidating the mechanisms underlying this effect could lead to novel targets for therapeutic intervention, and possibly to a better understanding of the pathophysiology of depression.

Cyclic AMP-CREB Signaling and Adult Neurogenesis

Antidepressants induce an acute increase in 5-HT and/or NE. Downstream of 5-HT and NE receptors, these drugs regulate intracellular signal transduction cascades and increase gene expression (Carlezon et al., 2005; Duman et al., 1997). One of the signaling pathways regulated by antidepressant treatment is the cAMP-CREB cascade. This second messenger pathway is up-regulated in the hippocampus at several levels by chronic antidepressant treatment, including increased levels of cAMP-dependent protein kinase and increased function and expression of the cAMP response element binding protein (CREB) (Nestler et al., 1989; Nibuya et al., 1996; Thome et al., 2000). A link between the cAMP-CREB pathway and neurogenesis has also been established. Administration of rolipram, an inhibitor of cAMP specific phosphodiesterase that is responsible for breakdown of cAMP, increases the proliferation and survival of neurons in the adult hippocampus, similar to the actions of antidepressant treatment (Nakagawa et al., 2002). Blockade of CREB function by expression of a dominant negative mutant decreases neurogenesis, further demonstrating a role for this transcription factor in the regulation of adult neurogenesis.

Neurotrophic/Growth Factors and Adult Neurogenesis

These studies of cAMP signaling and transcription factor function also indicate that specific gene targets underlie the induction of neurogenesis by CREB and antidepressant treatment. Neurotrophic/growth factors have been a focus of this work because of the neurotrophic hypothesis of depression (Duman, 2004a) and the role of these factors in the regulation of cell proliferation and survival during development, and the regulation of basal neurogenesis in the adult brain (Fig. 2). BDNF has been the target of initial studies because it is the first trophic factor found to be regulated by antidepressant treatment and is sufficient to produce antidepressant effects in behavioral models (Nibuya et al., 1995; Siuciak et al., 1997; Shirayama et al., 2002). Although infusions of BDNF into the lateral ventricles increase cell proliferation in number of brain regions, there is no effect on neurogenesis in the hippocampus (Pencea et al., 2001). Direct infusions of BDNF into the hippocampus also do not increase the proliferation of new neurons (Duman and colleagues, unpublished observations). A recent study has found that BDNF influences the survival of newborn neurons (Sairanen et al., 2005). This report demonstrates that the survival, but not proliferation, of newborn neurons was decreased in BDNF heterozygous null mutant mice, as well as a dominant negative TrkB mutant line, and that the antidepressant-induced increase in survival was blocked in these mutant lines. This study also shows that there is an up-regulation of cell death, as well as increased cell proliferation, indicating that there is an increase in cell turnover in response to antidepressant treatment.

VEGF is another factor that could underlie the neurogenic actions of antidepressants (Fig. 2): VEGF regulates basal rates of neurogenesis (Palmer et al., 2000), which is decreased by stress (Heine et al., 2005) and is up-regulated by ECS (Newton et al., 2003; Altar et al., 2004). Based on these observations, we have examined the role of VEGF in the actions of antidepressants (Warner and Duman, 2005). We have found that the time course for ECS-induction of VEGF in the GCL is consistent with the time course for induction of neurogensis, and that VEGF expression is up-regulated by chemical antidepressants. Moreover, the results demonstrate that VEGF is sufficient to increase neurogenesis, and that VEGF signaling is necessary for the neurogenic actions of antidepressant treatment. We have also found that infusion of VEGF into the lateral ventricles increases neurogenesis in the hippocampus, consistent with a recent qualitative report (Jin et al., 2002). Moreover, blockade of VEGF signaling blocks the up-regulation of neurogenesis in response to ECS as well as chemical antidepressants, including both 5-HT and NE selective reuptake blockers. These studies examined the cell proliferation phase of neurogenesis, and demonstrate that VEGF infusion increases proliferation and that blockade of VEGF signaling inhibits the induction of proliferation by antidepressant treatment. Taken together, these studies demonstrate that antidepressant treatment recruits VEGF and BDNF signaling to increase the proliferation and survival, respectively, of newborn neurons in the adult hippocampus (Fig. 2). VEGF is also required for the induction of neurogenesis in response to exercise (Fabel et al., 2003). These findings suggest a role for endothelial-derived VEGF in the actions of antidepressant treatment, although VEGF is also expressed in neuronal cells of the hippocampus (Fig. 3) (Newton et al., 2003). Release of VEGF could stimulate receptors located on both endothelial and neural progenitor cells and could thereby increase proliferation of both cell types, providing further support for differentiation and survival from other endothelial derived factors (Fig. 3).

In addition to VEGF and BDNF, other neurotrophic/growth factors have been identified by microarray analysis of ECS-induced gene expression in the hippocampus (Altar et al., 2004; Newton et al., 2003). Some of these factors, for example basic fibroblast growth factor-2 (FGF2), are known to be progenitor cell mitogens (Kuhn et al., 1996), and could also contribute to antidepressant regulation of neurogenesis. A recent report also demonstrates that the FGF2 system is altered in postmortem tissue of depressed subjects (Evans et al., 2004). In addition, there are other factors, such as insulin-like growth factor-1 (IGF-1), that are regulated by antidepressant treatment (Khawaja et al., 2004) and are involved in the up-regulation of neurogenesis by exercise (Trejo et al., 2001) that could also be involved in the actions of antidepressant treatment. Therefore, these additional factors identified by high-throughput microarray screens and

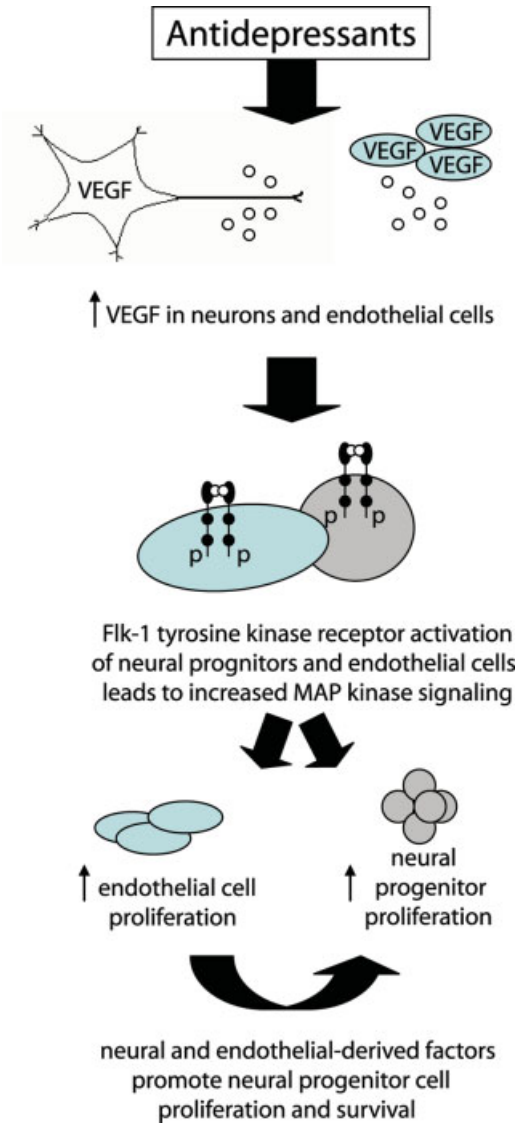

FIGURE 3. A model depicting possible cellular mechanisms for antidepressant regulation of VEGF and BDNF signaling and adult neurogenesis. Recent studies demonstrate that blockade of VEGF signaling blocks the induction of neurogenesis by antidepressant treatment. This indicates that the synthesis and release of VEGF from endothelial cells (shaded cells at the top) plays a role in the actions of antidepressants. It is also possible that neuronal VEGF is another source of this factor. In either case, the release of VEGF would then lead to stimulation of the Flk-1 receptor, one of several VEGF receptors linked to cell proliferation, which is located on both endothelial and neural progenitor cells. This could in turn lead to further release of endothelial-derived factors, including BDNF, which promotes the differentiation and survival of newborn neurons. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

basic studies of neurogenesis make up a list of interesting targets for further analysis in the actions of antidepressants.

Developmental Factors Involved in Adult Neurogenesis

Another avenue of investigation towards the underlying mechanism of antidepressant-induced neurogenesis involves the study of factors that were first characterized for their role in developmental neurogenesis. Some of these signaling pathways, including wingless (Wnt), sonic hedgehog (Shh), and others, have been implicated in the regulation of neurogenesis in the adult brain (Lai et al., 2003). Evidence for a role of these pathways has been provided by recent studies. One report has shown that ECS increases the expression of Wnt-2 and nuclear levels of β-catenin in the hippocampus (Madsen et al., 2003). β-catenin is a downstream effector of the Wnt signaling pathway that mediates progenitor cell proliferation and neural differentiation (Li and Pleasure, 2005). A recent study has also demonstrated a role for Shh, reporting that a pharmacological inhibitor of Shh signaling blocks the induction of neurogenesis by ECS (Banarjee et al., 2005). These factors, as well as others involved in the regulation of neurogenesis during development, represent additional mediators that could contribute to the mechanism of antidepressant-induced neurogenesis. Further studies of the role of these pathways in the actions of chemical antidepressants are necessary to test this hypothesis.

FUTURE STUDIES

Our understanding of the role of the hippocampus in depression and antidepressant treatment is at an early stage. Antidepressants reproducibly increase neurogenesis, but there are numerous unanswered questions that need to be addressed. For example, what is the cellular distribution of VEGF and BDNF, as well as other factors, in the hippocampus and what are the mechanisms that control the release and function of these factors in response to antidepressant treatments? What are the signal transduction pathways that control neurogenesis, and is there convergence of the pathways for these different growth factors? The influence of antidepressant treatment on the cAMP-CREB cascade has been discussed and a direct link with neurogenesis has been demonstrated (Fig. 4). The role of the signaling cascades activated by neurotrophic, growth, and angiogenic factors in the actions of antidepressant treatment have not been examined. These factors activate a number of pathways, including the MAP kinase, the phosphatidyl inositol-3 kinase (PI3K), and phospholipase-g (PLC-γ) pathways (Fig. 4). Additional studies will be needed to further define the role of these signaling pathways in the neurogenic actions of antidepressants, as well as the down-regulation of neurogenesis by stress.

A direct link between neurogenesis and the behavioral actions of antidepressants has been made (Santarelli et al., 2003), but additional work needs to be done and better models of depression will be needed to further test this hypothesis. Transgenic approaches are being developed to express cell cycle inhibitors, specifically in neural progenitors, as well as other strategies, to prevent newborn cell proliferation or neuronal differentiation without killing other cell types. These approaches will give us the tools we need to further address this important question.

A direct link between neurogenesis and depression will require postmortem analysis of hippocampal tissue from depressed subjects. Basic research has identified endogenous markers of cell proliferation, including Ki67, which could aid in the study of

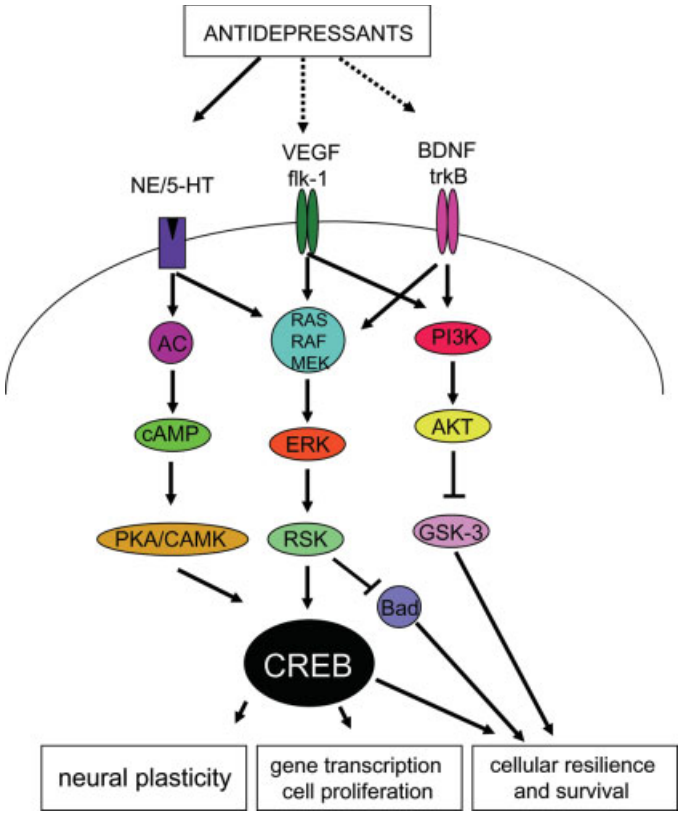

FIGURE 4. Converging signal transduction cascades regulated by monoamines and trophic factors. The monoamines NE and 5-HT regulate a number of second messenger systems, including the cAMP-CREB cascade. The formation of cAMP is mediated by adenylyl cyclase, and the actions of cAMP by cAMP-dependent protein kinase. The pathways regulated by BDNF and VEGF include the MAP kinase and PI3K cascades. The MAP kinase pathway is one of the best characterized and includes tyrosine autophosphorylation of the receptors, coupling with intracellular proteins and activation of a series of kinases, including RAF, MEK, ERK, and RSK, the latter capable of phosphorylating and activating CREB, as well as Bad and other cellular proteins. Key elements of the PI3K pathway include AKT, a serine/threonine kinase also known as protein kinase B, which block glycogen synthase kinase-3 (GSK-3) and regulates other proteins that promote cell survival and resilience pathways. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

neurogenesis in postmortem tissue from depressed patients. Since neurogenesis is influenced by other factors, including age (Kuhn et al., 1996), alcohol (Nixon and Crews, 2002) and exercise (van Praag et al., 1999), it will be a challenge to interpret these data. The studies conducted to date and reviewed here have given rise to these and other questions, and the possibilities for future research are exciting.

SUMMARY AND CONCLUSIONS

Depression is a complex disorder that targets more than one region of the brain, but there is compelling evidence for the involvement of the hippocampus in the action of antidepressants and in the underlying pathophysiology of depression. Since the hippocampus is most often studied for its involvement in learning and memory, antidepressants could exert their therapeutic effect by increasing plasticity to promote learning of new coping strategies and ways to deal with the stress and symptoms of depression. However, the hippocampus is also indirectly involved in the regulation of mood and cognition, suggesting that its role in depression could be more complex. Clinical studies demonstrate reduced hippocampal volumes in patients with depression and reversal of volumetric deficits by antidepressant treatment. Preclinical studies suggest that stress and antidepressants differentially regulate neurogenesis in the adult hippocampus, and in some studies, antidepressants prevent or reverse the damaging effects of stress on this structure. A role for neurotrophic, growth, and angiogenic factors in the neurogenic and behavioral actions of antidepressants lend further support to a neurotrophic and neurogenic hypothesis of depression. Evidence points towards a direct link between neurogenesis and the therapeutic action of antidepressants, but this hypothesis requires further testing. This work demonstrates a major conceptual shift in how we think about the causes of depression and the actions of antidepressant treatment, and represents an exciting period for the field. However, this work has raised many new questions and additional studies are needed to further characterize, identify, and validate the role of neurogenesis in depression.

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