Studies at the basic and clinical levels demonstrate that neuronal atrophy and cell death occur in response to stress and in the brains of depressed patients. Although the mechanisms have yet to be fully elucidated, progress has been made in characterizing the signal transduction cascades that control neuronal atrophy and programmed cell death and that may be involved in the action of antidepressant treatment. These pathways include the cyclic adenosine monophosphate (cAMP)–cAMP response element–binding protein (CREB) and neurotrophic factor–mitogen-activated protein (MAP) kinase cascades) also supports the notion of this relationship. The possibility that failure of neural plasticity could contribute to neurodegenerative disorders has recently been suggested (Finkbeiner 2000; Mesulam 1999). This review briefly discusses the background literature for a neuronal atrophy and cell death hypothesis of depression. Discussed in more detail are some of the intracellular cascades and target genes that control neuronal survival and plasticity and that could contribute to the actions of antidepressant agents.

Neuronal Atrophy and Death in Stress and Depression

Recent basic and clinical studies have provided direct evidence of neuronal atrophy and loss in response to stress and depression. These studies are discussed in detail in other reviews found in this issue and will only be briefly mentioned here (also see Duman et al 1999). Basic research studies have demonstrated that stress can result in atrophy and death of CA3 pyramidal neurons in the hippocampus (Table 1; see McEwen 1999; Sapolsky 1996). In addition, stress decreases the neurogenesis of dentate gyrus granule neurons in the hippocampus of adult animals (Gould et al 1997, 1998). These damaging effects of stress could contribute to the reduction of hippocampal volume reported in patients with depression or posttraumatic stress disorder (Bremner et al 1995; Drevets et al 1997; Sheline et al 1996); however, there are no reports to date that directly demonstrate a reduction in the number of neurons in hippocampus. This point needs to be addressed with additional postmortem analysis of cell number using unbiased stereological procedures.

In contrast, recent postmortem studies have demonstrated that the number of neurons and glia are reduced in the cerebral cortical regions, including prefrontal cortex, of depressed patients (Table 1; Ongur et al 1998; Rajkowska et al 1999). In addition, one of these studies also found that the size of neurons in cortical areas was reduced (Rajkowska et al 1999). These studies demonstrate that cell loss and damage in depression are not restricted to the
Brain-derived neurotrophic factor, a major neurotrophic factor (BDNF) in the hippocampus (Smith et al 1995).

decrease the expression of brain-derived neurotrophic dentate gyrus have not been determined.

coids decrease the neurogenesis of granule cells in the infection. The mechanisms by which stress or glucocorticoids damage certain populations of stress-vulnerable neurons (McEwen 1999; Sapolsky 1996). These studies demonstrate a role for glutamate excitotoxicity and a reduction in metabolic capacity, the latter resulting from a reduction in glucose uptake. Prolonged exposure to stress or glucocorticoids could be sufficient to produce cell damage via these mechanisms. Another possibility is that these effects could produce a state of neuroendangerment whereby cells become more vulnerable to other types of insult, such as hypoxia–ischemia, hypoglycemia, or viral infection. The mechanisms by which stress or glucocorticoids decrease the neurogenesis of granule cells in the dentate gyrus have not been determined.

In addition to these effects, stress is also reported to decrease the expression of brain-derived neurotrophic factor (BDNF) in the hippocampus (Smith et al 1995). Brain-derived neurotrophic factor, a major neurotrophic factor in the brain, is critical for the survival and guidance of neurons during development, but is also required for the survival and function of neurons in the adult brain (McAllister et al 1999; Thoenen 1995). For example, BDNF has been demonstrated to play a critical role in long-term potentiation, a cellular model of learning and memory, demonstrating that this neurotrophic factor can influence plasticity (Figurov et al 1996; Korte et al 1995). Decreased levels of BDNF in response to stress could lead to a loss of normal plasticity and eventually damage and loss of neurons. Reduction in BDNF expression, which is activity dependent, also suggests that neuronal activity may be decreased by stress, although there is no evidence for this to date. Assuming that this is the case, it is notable that a reduction in neuronal activity could contribute to the damaging effects of stress by reducing the survival of neurons (see below).

**Table 1. Stress and Depression Result in Neuronal Atrophy and Cell Death in the Cerebral Cortex and Hippocampus**

<table>
<thead>
<tr>
<th>Prefrontal cortex</th>
<th>Decreased number and size of neurons in depressed patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Decreased number of glia in depressed patients</td>
</tr>
<tr>
<td></td>
<td>Decreased volume of the subgenual prefrontal cortex</td>
</tr>
<tr>
<td></td>
<td>Influence of stress has not been determined</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>Decreased number and size of rodent CA3 neurons caused by exposure to stress</td>
</tr>
<tr>
<td></td>
<td>Decreased neurogenesis of rodent granule cells caused by exposure to stress</td>
</tr>
<tr>
<td></td>
<td>Decreased volume of the hippocampus in depressed patients</td>
</tr>
<tr>
<td>Stereological analysis of cell number in the hippocampus of depressed patients has not been determined</td>
<td></td>
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See text for references.

hippocampus. In addition, a reduction in the number of glia indicates that the loss of neurons is probably not the result of an inflammatory response, which would be expected to result in the opposite effect on the number of glia. These results suggest that neuronal loss may have occurred long before the time of death, possibly during the developmental period. Alternatively, this type of neuronal loss could result from programmed cell death or apoptosis. Additional basic research studies of the prefrontal cortex are required to determine if stress could produce similar effects and to investigate the cellular mechanisms responsible for cell loss.

**Cellular Actions of Stress**

There are many possible mechanisms that could contribute to the atrophy and loss of neurons observed in response to stress and depression. Although there is still a great deal that is not known, significant progress has been made in our understanding of how stress and adrenal glucocorticoids damage certain populations of stress-vulnerable neurons (McEwen 1999; Sapolsky 1996). These studies demonstrate a role for glutamate excitotoxicity and a reduction in metabolic capacity, the latter resulting from a reduction in glucose uptake. Prolonged exposure to stress or glucocorticoids could be sufficient to produce cell damage via these mechanisms. Another possibility is that these effects could produce a state of neuroendangerment whereby cells become more vulnerable to other types of insult, such as hypoxia–ischemia, hypoglycemia, or viral infection. The mechanisms by which stress or glucocorticoids decrease the neurogenesis of granule cells in the dentate gyrus have not been determined.

Activity-induced survival and growth of neurons could occur by several possible mechanisms (for complete references see Goldberg and Barres 2000). First, an increase in the number of synaptic connections and neuronal activity could elevate the expression of neurotrophic factor in the postsynaptic cells. This type of activity-dependent expression has been reported in many systems and for several different neurotrophic factors, including BDNF. Second, an increase in the number of synaptic connections could result in increased supply of neurotrophic factor from the presynaptic terminal. For example, BDNF is transported in an anterograde manner from dentate gyrus granule neurons to CA3 pyramidal neurons. Third, depo-
larization or activation of the cAMP cascade in postsynaptic neurons could increase the neuronal responsiveness to neurotrophic factor stimulation. Activity-dependent expression of BDNF and other neurotrophic factors could have relevance to the atrophy and loss of neurons in depressed patients (see below).

**CREB and Neurotrophic Factor–Mediated Neuronal Survival**

The process of programmed cell death includes shrinkage of neurons, condensation of chromatin, and finally complete cell disintegration (Nijhawan et al 2000). Although it was originally thought that neurotrophic factors increased cell survival by providing necessary trophic support, it is now clear that their survival-promoting effects are mediated by inhibition of the cell death pathway. Programmed cell death is controlled by factors that either promote or inhibit the cell death pathway. Proteins that are required for programmed cell death are the caspases, a family of cysteine proteases. Caspases are activated by proteolytic cleavage, resulting in degradation of cellular proteins that are necessary for neuronal survival. Conversely, other factors, the Bcl-2–like proteins, inhibit the cell death pathway, and thereby increase neuronal survival. Bcl-2 prevents cell death by inhibiting pathways that activate caspases; however, another member of this group, Bad, blocks the actions of Bcl-2 and thereby promotes cell death.

Recent studies have elucidated the mechanisms that underlie neurotrophic factor inhibition of cell death (Figure 1; Finkbeiner 2000). These mechanisms include regulation of both Bcl-2 and Bad. One of the intracellular pathways activated by neurotrophic factor coupled trk receptors is the MAP kinase cascade (Russell 1995). Interestingly, recent studies demonstrate that one of the targets of this pathway is CREB (Finkbeiner 2000). Activation of CREB via the MAP kinase cascade is mediated by ribosomal S6 kinase (Rsk). Thus, in addition to activation by cAMP-dependent protein kinase, as well as other second messenger–dependent protein kinases (protein kinase C and calcium/calmodulin-dependent protein kinase), CREB can be phosphorylated and activated by Rsk.

The question as to how Rsk-2 and CREB mediate the survival or anti-apoptotic actions of neurotrophic factors has been addressed by two elegant studies (Figure 1; Bonni et al 1999; Riccio et al 1999). In one of these studies (Bonni et al 1999) BDNF-induced survival of cerebellar granule cells was found to be dependent on activation of Rsk and two important actions of this kinase. First, activated Rsk increases the phosphorylation of Bad, and thereby inactivates this cell death factor. Second, Rsk...
increases the phosphorylation of CREB, resulting in up-regulation of the expression of Bcl-2, which inhibits cell death pathways. Riccio and colleagues (1999) also demonstrated a requirement for CREB and upregulation of Bcl-2 expression in neurotrophic factor–mediated survival of sympathetic neurons or cerebral cortical neurons. The promoter of the Bcl-2 gene contains a CRE that confers responsiveness to CREB, although additional transcription factors are thought to be required for induction of Bcl-2 expression (Finkbeiner 2000).

It is conceivable that the cell loss observed in depression could result from alterations in the factors that control programmed cell death (e.g., increased Bad or decreased Bcl-2–like proteins) and the pathways that control the function and expression of these proteins (e.g., decreased Rsk and CREB). One study has already reported that levels of CREB are decreased in the cerebral cortex of depressed patients (Dowlatshahi et al 1998). Additional studies are needed to confirm this finding and to examine other proteins involved in cell survival and plasticity.

**Antidepressant Treatment Upregulates the cAMP-CREB Cascade and Expression of BDNF**

Recent studies demonstrate that antidepressant treatment upregulates the cAMP–CREB cascade and expression of BDNF (Figure 2; Duman et al 1999). Regulation of the cAMP–CREB cascade includes increased coupling of the stimulatory guanosine triphosphate (GTP)–binding protein (G_s) to adenylyl cyclase, increased particulate levels of cAMP-dependent protein kinase (PKA), and CREB. CREB can also be phosphorylated by Ca^{2+}-dependent protein kinases, which can be activated by the phosphatidylinositol pathway (not shown) or by glutamate ionotropic receptors (e.g., N-methyl-D-aspartate [NMDA]). Glutamate receptors and Ca^{2+}-dependent protein kinases are also involved in neural plasticity. One gene target of antidepressant treatment and the cAMP–CREB cascade is brain-derived neurotrophic factor (BDNF), which contributes to the cellular processes underlying neuronal plasticity and cell survival. BAR, β-adrenergic receptor; PDE, phosphodiesterase.
BDNF occurs in response to several different classes of antidepressant treatments, including norepinephrine (NE) and serotonin selective reuptake inhibitors and electroconvulsive seizure, indicating that the cAMP–CREB cascade and BDNF are common postreceptor targets of these therapeutic agents (Nibuya et al 1995, 1996). In addition, upregulation of CREB and BDNF is dependent on chronic treatment, consistent with the therapeutic action of antidepressants. A role for the cAMP–CREB cascade and BDNF in the actions of antidepressant treatment is also supported by studies demonstrating that upregulation of these pathways increases performance in behavioral models of depression (Duman et al 1999).

The mechanisms underlying the upregulation of CREB and BDNF are currently being studied. The promoter of the BDNF gene contains a CRE and has been shown to be induced by CREB (Shieh et al 1998; Tao et al 1998). The mechanisms underlying the regulation of CREB are less clear, but one model we have proposed is that antidepressant treatment increases the phosphorylation and expression of CREB via activation of cAMP-dependent protein kinase and Ca$^{2+}$-dependent kinases. This could occur via NE and serotonin receptors and the corresponding second messenger pathways, the cAMP and phosphatidylinositol cascades, which stimulate these kinases. Activation of Ca$^{2+}$-dependent kinases via glutamate receptors could also contribute to the regulation of CREB phosphorylation (Figure 2). Evidence for antidepressant regulation of N-methyl-D-aspartate–glutamate receptors has been reported (Paul et al 1994). It is also possible that antidepressant- and/or monoamine-induced upregulation of CREB could occur via activation of the MAP kinase pathway and Rsk. Recent studies demonstrate that activation of G protein–coupled receptors, including β-adrenergic and serotonin$\text{_{1A}}$ receptors, can also activate the MAP kinase cascade (Luttrell et al 1999; Mendez et al 1999). These findings provide a novel pathway by which the NE and serotonin neurotransmitter systems, and psychotropic drugs that act on NE and serotonin, could influence CREB and other intracellular targets.

Upregulation of CREB and BDNF raises the possibility that antidepressant treatment could oppose the cell death pathway. This could occur via increased expression of Bcl-2. Studies are needed to determine if antidepressant treatment increases Bcl-2 expression. Lithium treatment has been reported to increase the expression of Bcl-2 in brain and cultured cells, and inhibits apoptosis of cultured cerebellar granule neurons (Chen et al 1999; Chen and Chuang 1999; Nonaka et al 1998). These findings suggest that regulation of the cell death pathways could also contribute to the actions of agents used for the treatment of bipolar disorder. It is also possible that antidepressant treatment could influence the function of Rsk, another hypothesis that warrants future investigation. Direct studies of antidepressant inhibition of cell death are more complicated and would involve conditions where cell death occurs naturally or is induced. For example, does antidepressant treatment influence the cell death that occurs during development or is induced by other types of stimuli? Another possibility is to study the influence of antidepressants on cell death in genetic models where a gene mutation increases cell death (e.g., Bcl-2 null mutant mice).

**Antidepressant Treatment Increases Hippocampal Neurogenesis**

In addition to a potential role in cell survival, it is possible that antidepressant treatment also regulates other processes, such as neurogenesis, that could influence the number of neurons. Recent studies support this hypothesis and demonstrate that chronic, but not acute, antidepressant treatment increases the neurogenesis of dentate gyrus granule cells (Malberg et al 1999). These studies demonstrate that chronic administration of different classes of antidepressant treatment, including NE and serotonin selective reuptake inhibitors and electroconvulsive seizure, increases the proliferation and survival of new neurons. In contrast, increased neurogenesis is not observed in response to chronic administration of nonantidepressant psychotropic drugs.

Studies demonstrating that neurogenesis is increased by conditions that stimulate neuronal activity (e.g., enriched environment, learning, exercise) suggest that this process is also positively regulated by, and may even be dependent on, neuronal plasticity (Gould et al 1999a; Kempermann et al 1997; van Praag et al 1999). Indeed, there is also overlap of the pathways that mediate neurogenesis and neuronal plasticity. In vitro studies demonstrate that activation of the cAMP–CREB cascade or incubation with BDNF increases differentiation of new cells into neurons, but does not directly influence the division of progenitor cells (Palmer et al 1997). These findings suggest that upregulation of CREB and BDNF in response to antidepressant treatment could increase the differentiation and survival of neurons, but not cell proliferation. Increased differentiation could occur via a direct effect on the immature cells, depending on whether or not the cells express the appropriate NE and serotonin receptors. Our preliminary studies are consistent with this hypothesis. We have found that new cells express very low levels of CREB, but as they mature they express higher levels of CREB and an increase in its phosphorylation, demonstrating that CREB is activated (unpublished results). Regulation of cell proliferation could involve a different mechanism. One possibility is that there are other cell types...
located in the vicinity of the progenitor cells that are activated by antidepressant treatment and that release a proliferation factor onto the progenitor cells. Studies are currently underway to identify proliferation factors that could be regulated by CREB and could mediate the action of antidepressants.

Upregulation of granule cell neurogenesis could be one mechanism by which antidepressant treatment increases neuronal number in hippocampus. Increased granule cell neurogenesis could also influence the survival and function of the CA3 neurons that receive input from the granule cells. This could occur via increased synaptic input and depolarization-induced survival of CA3 neurons, and increased levels of BDNF that is supplied by anterograde transport from granule cells. A recent study demonstrating that neurogenesis also occurs in the cerebral cortex (Gould et al 1999b) raises the possibility that the cell loss in the cerebral cortex of depressed patients could result from decreased neurogenesis. Studies to determine the influence of stress and antidepressants on cortical neurogenesis are needed to test this hypothesis.

**Neural Plasticity and Cell Survival**

It is notable that CREB and BDNF have also been demonstrated to play a critical role in neural plasticity, particularly in cellular and behavioral models of learning and memory (Figurov et al 1996; Korte et al 1995; Silva et al 1998). Taken together, these studies demonstrate that there is considerable overlap between the intracellular pathways that mediate neuronal depolarization and neural plasticity and those that control cell survival (Figure 3). In addition to BDNF and CREB, it is likely that there are other convergent factors that mediate the actions of neural plasticity and cell death. This has resulted in the hypothesis that cellular activity and plasticity is a necessary requirement for neuronal survival. As mentioned above, increased synaptic activity could promote cell survival via a number of mechanisms, including increased amounts of, and responsiveness to, neurotrophic factors.

The possibility that failure of the mechanisms underlying neural plasticity could contribute to neurodegenerative disorders has been discussed (Mesulam 1999). We would like to extend this model and propose a hypothesis that stress-related affective illnesses, as well as other psychiatric disorders, result in part from a loss of neuronal plasticity. For example, it is possible that the atrophy and loss of neurons in depressed patients may result from a reduction in the normal level of synaptic activity. This could be combined with stress-induced loss of neurotrophic factors, or other factors that compromise neuronal function and activity (e.g., hypoxia–ischemia, hypoglycemia, viral infections). Another possibility is that there are genetic factors, including mutations of the genes encoding intracellular signaling proteins, that influence neural plasticity.

Support for this hypothesis is provided by brain imaging studies. Reduced blood flow, which suggests decreased neuronal activity, has been reported in prefrontal regions when sadness is induced in healthy individuals (Mayberg 1997). In addition, relapse of depressive symptoms is reported to decrease metabolism in the dorsolateral prefrontal cortex (Bremner et al 1997). These findings suggest that sadness and depression induce a reduction in neuronal activity in the prefrontal cortex. It is possible that...
if this type of hypofunction is sustained for a long period of time it could result in a loss of activity-induced neurotrophic factors in this brain region. This could contribute to the reduction in volume and cell size and number that has been reported in depressed patients (Drevets et al 1997; Ongur et al 1998; Rajkowska et al 1999).

**Development of Novel Therapeutic Agents**

Studies demonstrating that an upregulation of the cAMP–CREB cascade is involved in the action of antidepressant treatment provide one set of novel targets for development of therapeutic agents. This includes the agents that act on the receptors that are directly coupled to the cAMP cascade (e.g., the serotonin7 receptor) or that could directly increase levels of cAMP (e.g., selective inhibitors of cAMP phosphodiesterase [PDE4] isozymes). These possibilities are discussed in detail in previous reviews (Duman et al 1997, 1999). Other targets of interest are the various components of the MAP kinase and cell death pathways. It is possible that agents that activate the MAP kinase pathway or Rsk could promote cell survival and have antidepressant efficacy. Further studies are needed to validate these targets and to utilize available inhibitors and activators of the MAP kinase cascade to test this possibility.

**Summary and Conclusions**

The studies discussed in this review raise the possibility that atrophy and cell death are intimately related to synaptic interactions between neurons and normal processes of neuronal plasticity. Failure of these processes and loss of synaptic interactions could contribute to a loss of neurotrophic factor input to neurons that could eventually lead to further atrophy and death of neurons. Failure of neuronal plasticity could result from disruption of signaling processes at a number of levels, including the cAMP–CREB and neurotrophic factor–MAP kinase cascades; however, this is only a partial list of the complex array of intracellular signaling systems in the brain, and future studies are required to further elucidate the role of these pathways in depression. In addition, disruption of these processes could occur via environmental stimuli that compromise a cell’s ability to undergo neuronal plasticity. These findings lend support to the notion that affective disorders, as well as other psychiatric disorders, could result from a failure of plasticity. This hypothesis could be tested by brain imaging studies that characterize the brain regions where a reduction in neuronal activity occurs in response to thought processes related to depression or other disorders. In addition, this model could be further tested by a combination of behavioral and pharmacologic interventions that correct or produce normal levels of neuronal activity in the affected brain regions. This hypothesis also supports the possibility that other types of neuronal insult (e.g., those resulting from cardiovascular disease) could explain their high rate of depression associated with these illnesses (Duman et al 1997).

The authors acknowledge the support of the U.S. Public Health Service (Grants Nos. MH45481, MH53199, and 2 PO1 MH25642), the Veterans Administration National Center Grant for PTSD, VA Medical Center, and the National Alliance for Research on Schizophrenia and Depression.

Aspects of this work were presented at the conference “Depression in the Twenty-First Century: New Insights into Drug Development and Neurobiology,” February 21–22, 2000, Dana Point, California. The conference was sponsored by the Society of Biological Psychiatry through an unrestricted educational grant provided jointly by Pharmacia & Upjohn and Janssen Pharmaceutica.

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