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What is This?
Stress, Antidepressant Treatments, and Neurotrophic Factors: Molecular and Cellular Mechanisms

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Repeated stress or an excess of glucocorticoids can exacerbate neuronal damage in response to insults and, in severe cases, can lead to neuronal atrophy and death. These effects are thought to be related to the actions of stress and glucocorticoids on glutamate function, neuronal metabolism, and the generation of cytotoxic free radicals. Recent studies demonstrate that the regulation of neurotrophic factors may contribute to the actions of stress on neuronal function. Acute or chronic stress decreases the expression of brain derived neurotrophic factor, the most abundant neurotrophin in the brain, in specific regions of the hippocampus, and other forebrain regions. In addition, chronic stress increases the expression of neurotrophin-3 in certain regions of the hippocampus and may, thereby, help to protect these regions from the neurotoxic effects of chronic stress. The deleterious effects of stress may contribute to psychiatric illnesses, such as depression, that can be precipitated or worsened by stress and that are often characterized by hypercortisolism. Electroconvulsive seizure therapy, as well as antidepressant drugs, increase the expression of brain derived neurotrophic factor and its receptor, trkB, in the brain, demonstrating that neurotrophins are a target of antidepressant treatments. These findings outline a role of neurotrophic factors in the etiology and treatment of certain psychiatric illnesses.

KEY WORDS Brain derived neurotrophic factor, Glutamate, Hippocampus, Electroconvulsive seizure, Cell survival, Atrophy

Exposure to stress results in the activation of several neurotransmitter pathways (e.g., norepinephrine, serotonin, dopamine, and glutamate) and neuroendocrine systems, most notably the hypothalamic-pituitary-adrenal axis, which are designed to prepare an animal for fight or flight responses. However, severe, traumatic stress or repeated exposure to stress can result in long-term deleterious effects, including even cell atrophy and death, which result in behavioral abnormalities. For example, stress is thought to precipitate or exacerbate several psychiatric illnesses, including depression, posttraumatic stress disorder, and schizophrenia. Advances in basic research demonstrate that many of the deleterious effects of stress on neuronal systems may result from complex interactions between neurotransmitters, hormones, and neurotrophins at the cellular level. This review will discuss the influence of stress and adrenal-glucocorticoids on neuronal survival and function and the potential role of neurotrophic factors in these actions. In addition, the influence of neurotrophic factors on serotonin and norepinephrine, two neurotransmitter systems involved in the manifestation and treatment of depression and other affective illnesses, and the role of neurotrophic factors in the actions of antidepressant treatments will be discussed.

Influence of Stress and Glucocorticoids on Neuronal Survival and Growth

The neurochemical and morphological effects of stress and high levels of adrenal-glucocorticoids have been best characterized in the subfields of the hippocampus. In certain subfields, the neurons are vulnerable to stress and excess glucocorticoids and cell survival may be decreased. In other subfields, the neurons are more resistant to stress and glucocorticoids and their survival is dependent on the presence of glucocorticoids. This work and the possible mechanisms underlying the actions of stress and glucocorticoids are briefly reviewed (1–4).
Stress-induced Atrophy and Survival of Hippocampal Neurons

The hippocampus, due to high levels of both type I and II glucocorticoid receptors, is one of the primary targets of stress and adrenal steroids in the brain. The effects of stress and adrenal-glucocorticoid treatments are not uniform across the different pyramidal fields and dentate gyrus (Fig. 1). Severe chronic stress or prolonged exposure to glucocorticoids has been shown to cause cell loss and atrophy of the pyramidal neurons in the CA fields, prominently in the CA3 region, whereas the granule cells of the dentate gyrus are relatively resistant to damage by these treatments (5, 6). Dendritic atrophy of CA3 pyramidal neurons, characterized by the decreased number and length of apical dendrites, occurs in response to repeated restraint stress or glucocorticoid treatment (7, 8). In addition, stress or glucocorticoid treatments can exacerbate the loss of hippocampal neurons in response to other insults, such as excitotoxins, hypoxia-ischemia, and hypoglycemia (1, 2, 9). The influence of stress and glucocorticoids on the survival of neurons in other brain regions has not been studied, but it is possible that similar effects occur on select populations of neurons throughout the brain.

Although stress and high levels of adrenal-glucocorticoids lead to neuronal atrophy of CA3 neurons, the survival and the function of other neurons in the hippocampus are dependent on the presence of glucocorticoids. This effect is most prominent in the dentate gyrus, where removal of adrenal-glucocorticoids (i.e., adrenalectomy) leads to degeneration and death of granule cells (Fig. 1) (10–13). Long-term adrenalectomy is also reported to cause degeneration of CA4 pyramidal neurons. Although the exact mechanisms by which glucocorticoids influence cell survival in the hippocampus are not known, the regulation of cell cycling may be involved. Granule cells of the dentate gyrus continue to undergo cell birth and death and thereby maintain a relatively static number of cells in the presence of normal physiological levels of glucocorticoids (11, 12). The absence of glucocorticoids enhances cell birth and death, but cell death proceeds at a faster rate and eventually leads to fewer healthy cells. This process can be reversed by glucocorticoid replacement (10–12).

![Fig. 1. Schematic diagram of the hippocampus and the influence of stress on the growth and survival of individual populations of neurons. The CA pyramidal neurons, including CA1 and CA3, and the dentate gyrus granule cells comprise the primary cell groups in the hippocampus. Afferent pathways from the granule cells to CA3 (mossy fiber pathway) and from CA3 to CA1 (Schaffer collateral) provide connections within the hippocampus. Exposure to stressful stimuli leads to several effects that may contribute to the atrophy and death of CA3 pyramidal neurons. This includes decreased expression of BDNF in CA3 and CA1 neurons, which would reduce the autocrine and target derived sources of this neurotrophin, respectively. CA3 neurons also lack Ca²⁺ binding proteins. These characteristics may contribute to increased sensitivity of CA3 neurons to the deleterious effects of stress and glucocorticoids (GCs), including enhanced vulnerability to glutamate neurotoxicity and atrophy of apical dendrites. In contrast, the dentate gyrus granule cells express Ca²⁺ binding proteins (calbindin-D28k and parvalbumin) and the protective protein, bcl-2, that may make these neurons more resistant to the damaging effects of stress and other neuronal insults. In addition, although stress decreases levels of BDNF in granule cells, chronic, but not acute, stress increases levels of NT-3, which may also contribute to the resistance of these neurons.](image-url)
findings indicate that neuronal survival and function is dependent on the appropriate balance of glucocorticoid levels.

**Cellular and Neurochemical Mechanisms of Stress-induced Atrophy and Death of Neurons**

The neurotoxic effects of stress and excess glucocorticoids on CA3 pyramidal neurons is thought to involve increased activation of glutamatergic pathways (Fig. 1) (1). It has been suggested that chronic exposure to stress and glucocorticoids may increase the firing rate of dentate granule cells, because adrenalectomy decreases granule cell survival and activity (1). Granule cell mossy fibers synapse on CA3 pyramidal neuron apical dendrites, and increased activity of this pathway could enhance the release of glutamate at these synapses, leading to the reported atrophy of apical dendrites. In support of this hypothesis, stress does not influence pyramidal neuron basal dendrites, which do not receive mossy fiber inputs. CA3 pyramidal neurons also lack calcium binding proteins, like parvalbumin and calbindin-D28k, which could compromise the ability of these neurons to handle excess calcium (14), and do not express the neuroprotective protein, bcl-2 (15). Interestingly, neurotrophins are reported to increase the expression of calbindin in primary hippocampal cultures (16, 17).

The neurotoxic effects of stress may also involve glucocorticoid-enhancement of glutamate and the loss of the homeostatic control of free cytosolic calcium (1, 2, 9). Glucocorticoids are known to increase levels of glutamate in response to seizure, to inhibit glutamate reuptake by neurons and glia, to increase intracellular calcium in response to glutamate, and to increase calcium-dependent proteolysis. The neurotoxic actions of glucocorticoids are also related to glucocorticoid inhibition of glucose uptake, which compromises the metabolic capacity of the neurons. In this compromised state, the neurons are unable to counter the effects of increased intracellular calcium. Glucocorticoids also influence the generation of free radicals that contribute to cellular damage. These findings indicate that any combination of stress or excess glucocorticoids, along with exposure to neuronal insult, could be neurotoxic and lead to atrophy and cell death.

The action of glucocorticoid treatments on cell survival may involve regulation of other neurotransmitters, such as serotonin. Atrophy of dendrites and loss of synapses in the hippocampus, as well as other brain regions, in response to serotonin selective neurotoxins is partially reversed by glucocorticoid treatment (18, 19). This effect of glucocorticoids may occur via increased expression of tryptophan hydroxylase, the rate-limiting enzyme for serotonin synthesis. In addition, administration of a selective serotonin agonist for the 5-HT1A receptor partially reverses the loss of synapses and dendrites resulting from neurotoxin treatment (19).

These findings suggest that the maintenance of neuronal growth and survival may be dependent, in part, on the presence of serotonin.

**Alterations of Hippocampal Function and Volume in Affective Illnesses**

The hippocampus contributes to feedback inhibition of the hypothalamic-pituitary-adrenal axis via a multisynaptic pathway (20, 21). Glucocorticoid-mediated loss of hippocampal neurons would lead to loss of this inhibitory input: such a cycle would be self-perpetuating and would contribute to enhanced and sustained hypercortisolism. There is some evidence that this may occur in humans. Young and colleagues (22) demonstrated a loss of hippocampal feedback inhibition of the hypothalamic-pituitary-adrenal axis in depressed patients. In addition, Bremner and coworkers (23) reported that hippocampal volume is decreased in patients with posttraumatic stress disorder. Although the underlying nature of these findings is not known, the results are consistent with dysfunction or loss of hippocampal neurons in these stress related disorders.

**Stress and Adrenal Glucocorticoids Regulate the Expression of Neurotrophins**

Expression of neurotrophins contributes to the survival and growth of neurons. The neurotrophin family includes nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4/5. These neurotrophins bind to the trk receptors trkA, trkB, and trkC, which possess protein tyrosine kinase activity (24–26). Differential expression of these neurotrophins and their receptors may also contribute to the maintenance and survival of certain neuronal types in response to stress, as well as other types of neuronal insult. Studies demonstrating the regulation of neurotrophins by stress and adrenal glucocorticoids and the potential role of neurotrophins are discussed below.

**Stress Regulates Levels of Neurotrophins in the Hippocampus**

The potential role of neurotrophins in the actions of stress has been examined by Smith and colleagues (27, 28). Acute restraint (2 h) causes a rapid decrease in levels of BDNF mRNA in several regions of the hippocampus, most prominently in the dentate gyrus and CA3, an effect that has been replicated in our laboratory (Fig. 2). Repeated chronic stress (7 d) results in a similar degree of BDNF down-regulation in the dentate gyrus and CA3 and also decreases levels of BDNF mRNA in CA1. In contrast to down-regulation of BDNF, repeated, but not acute, stress increases the expression of NT-3. Up-regulation of NT-3 mRNA is most prominent in the dentate gyrus, with smaller effects observed in CA1 and CA2, and no increase observed in CA3. Stress did not influence the expression of the receptors for
Fig. 2. Regulation of BDNF by stress and electroconvulsive seizure. Acute restraint stress (top panel) decreases the expression of BDNF mRNA in the hippocampus and other brain regions. Rats were subjected to restraint stress for 2 hours, and BDNF mRNA was determined by in situ hybridization analysis, using a [35S]-labeled BDNF riboprobe. In contrast, acute ECS (bottom panel) increases the expression of BDNF as well as its receptor, trkB (not shown), in the brain. Rats received a single ECS stimulus, and levels of BDNF mRNA were determined 2 hours later. Shown are representative autoradiograms from sham, stress, and ECS treated rats.

BDNF or NT-3 and trkB and trkC or the expression of NT-4/5 in these studies.

Smith proposed that enhanced expression of NT-3 could replace the loss of BDNF in response to chronic stress and could thereby act in an autocrine fashion to help protect those neurons expressing NT-3 (Fig. 1). This would be consistent with the findings discussed above, that dentate gyrus granule cells are most resistant to the neurotoxic actions of stress and glucocorticoids. In addition, loss of autocrine and target derived BDNF could contribute to the sensitivity of CA3 neurons to chronic stress (Fig. 1). The replacement actions of NT-3 in the face of decreased levels of BDNF could occur via binding of NT-3 to its high affinity receptor, trkC, or via binding, albeit with lower affinity, to the trkB receptor. However, the role of BDNF and NT-3 in the atrophy and resistance of CA3 pyramidal neurons and dentate gyrus granule cells, respectively, remains to be determined. If decreased expression of BDNF contributes to the atrophy of CA3 neurons, it should be possible to rescue these neurons by replacement treatment with BDNF or even NT-3. Conversely, if granule cell resistance is due, in part, to up-regulation of NT-3, then removal of this neurotrophin, using antisense oligonucleotide or knockout strategies, should make these cells more vulnerable to stress and glucocorticoid treatments.

In addition to the hippocampus, chronic stress increases the expression of NT-3 in the cell bodies of locus coeruleus, the major noradrenergic cell nucleus in the brain (29). Locus coeruleus neurons are activated by acute and repeated stress, and repeated stress increases the expression of the cAMP signal transduction pathway and the levels of tyrosine hydroxylase, the rate limiting enzyme for catecholamine synthesis (30, 31). These effects of chronic stress are thought to represent a compensatory response to increased demand for noradrenaline synthesis and release in locus coeruleus neurons. Up-regulation of NT-3, which has been shown to increase the survival and function of locus coeruleus neurons (32), could contribute to the increased function of these neurons in response to chronic stress. For example, electrophysiological studies suggest that mild stress increases the innervation of cerebral cortex by locus coeruleus neurons (33). Conversely, loss of NT-3 could compromise the ability of locus coeruleus neurons to mount a compensatory response, such as increased expression of tyrosine hydroxylase, required to deal with chronic stress.

Role of Glucocorticoids in Regulation of Neurotrophins by Stress

The role of glucocorticoids in the regulation of BDNF and NT-3 by stress has been examined (29). In adrenalectomized rats, supplemented with low doses of exogenous glucocorticoids to approximate unstressed hormone levels, the influence of stress on the down-regulation of BDNF and the up-regulation of NT-3 was not significantly altered. However, adrenalectomy, in the absence of glucocorticoid supplement, significantly decreased the expression of NT-3, but not BDNF, in the dentate gyrus and CA2 of the hippocampus, suggesting that basal expression of NT-3 is dependent on the presence of adrenal glucocorticoids. To further examine the role of glucocorticoids, rats were administered high doses of glucocorticoids that approximate levels observed during stress. Acute glucocorticoid treatment (2 h) did not produce a rapid decrease in the levels of BDNF, like that observed after acute restraint stress. Repeated treatment (2 to 14 d) decreased the levels of BDNF, but this effect was very small relative to that observed after acute or chronic stress. Expression of NT-3 was not influenced by either acute or repeated glucocorticoid treatment. The results indicate that excess glucocorticoid levels can not fully explain the regulation of BDNF and NT-3 observed during stress, but that adrenal steroids may have a modulatory effect on neurotrophin expression (34, 35). Another possibility is...
that decreased expression of BDNF is mediated by other factors (e.g., neuropeptides, cytokines, or interleukins) that are released by stress (Fig. 3).

**Role of Neuronal Activity in the Regulation of Neurotrophins by Stress**

Regulation of neurotrophin expression by stress may be mediated by the level of neuronal activity and activation of stimulatory and/or inhibitory neurotransmitter systems (Fig. 3). Expression of BDNF is reported to be increased by neuronal activity and by several different neurotransmitter systems (25). For example, activation of glutamate receptors increases the expression of BDNF and NGF in the hippocampus, cerebral cortex, and other brain regions (36, 37). It is conceivable that stress regulates the expression of BDNF by decreasing stimulatory glutamatergic input. However, as discussed above, increased glutamate neurotoxicity is one hypothesis put forth to explain the atrophy observed in response to stress and glucocorticoid treatments. In addition, stress is reported to increase the levels of glutamate in the hippocampus, although this effect is significantly smaller than that observed in other brain regions (38). Taken together, the observations that stress increases glutamate but decreases expression of BDNF appear to be contradictory. However, it is possible that stress selectively activates glutamate pathways in specific subfields or neuronal subtypes in the hippocampus or that the glutamate increase is too small to stimulate BDNF expression. This possibility is supported by the reports that stress has little or no effect on the expression of c-fos in the hippocampus, which would be expected if the levels of glutamate were significantly increased (39). By contrast, stress significantly increases the expression of c-fos in the frontal cortex, a brain region where the elevation of extracellular glutamate is several-fold greater relative to the hippocampus and where there is no down-regulation of BDNF in response to stress.

Another possibility is that stress inhibits neuronal activity via the activation of the inhibitory neurotransmitter pathways (Fig. 3). For example, blockade of GABA, the major inhibitory neurotransmitter in the brain, increases the expression of BDNF (37), and administration of diazepam, a benzodiazepine that augments GABAergic function, completely blocks kainic acid induction of BDNF in the hippocampus (36). Stress could decrease neuronal activity via activation of inhibitory GABAergic pathways and thereby decrease the expression of BDNF. This possibility requires additional testing; for example, if this is true, GABA antagonists should selectively block the down-regulation of BDNF in response to stress.

Stress also increases levels of norepinephrine in the hippocampus and other brain regions (31), and it is possible that this monoamine exerts a modulatory effect on neurotrophin expression. However, norepinephrine is reported to increase BDNF expression in hippocampal primary cultures (40) and to mediate, in part, the induction of BDNF in response to seizures (41), suggesting that this neurotransmitter does not mediate the down-regulation of BDNF in response to stress.

**Stress, Neurotrophins, and Impairment of Memory**

One of the consequences of stress is inhibition of short-term memory and cognitive functioning (1-4). Given the role of the hippocampus in memory and cognition, it is possible that down-regulation of BDNF by stress could contribute to impaired memory and cognition. This possibility has been examined with an established cellular model of memory, long-term potentiation, and animal models of memory and cognition. In long-term potentiation, a brief stimulation of one of the primary afferent pathways in the hippocampus produces an increase in the excitatory potential of the postsynaptic cells, usually CA1 or CA3 pyramidal neurons. Long-term potentiation leads to an increase in the levels of BDNF (42). Because stress is reported to inhibit long-term potentiation (43), it is possible that stress-induced down-regulation of BDNF is involved in the loss of a potentiated response. In vivo studies demonstrate that expression of BDNF is associated with improved spatial memory in animals (44). In addition, cell death in aged and glucocorticoid-treated rats is correlated with impairment of cognitive performance (45).

**Antidepressant Treatments Regulate the Expression of Neurotrophins and Their Receptors**

The significant effects of stress and glucocorticoid treatments on dendritic atrophy and neuronal survival could also play a role in the pathophysiology and treatment of psychiatric disorders, such as depression, that are influenced by stress and often characterized by hypercortisolism. Moreover, the finding that stress decreases the expression of BDNF in several forebrain areas suggests that regulation of neurotrophins could contribute to the effects of stress on neuronal maintenance and survival. The ability of neurotrophins to influence the survival and function of neurotransmitter systems that are involved in depression (i.e., serotonin and norepinephrine) also suggests that neurotrophins could play a role in the manifestation and treatment of such disorders. Recent studies provide direct evidence for this possibility: Neurotrophins have antidepressant effects in behavioral models of depression, and antidepressant treatments influence the expression of neurotrophins.

**Neurotrophins Enhance Monoamine Neuronal Survival and Function**

Many antidepressant drug treatments acutely increase the synaptic levels of norepinephrine and serotonin by blocking their reuptake or metabolism (46, 47). How-
Fig. 3. Schematic diagram demonstrating the pathways for regulation of neurotrophins by stress, seizures (e.g., ECS), and antidepressant treatments. Acute or chronic stress decreases levels of BDNF in the hippocampus, but the mechanisms underlying this decrease are not known. Glucocorticoid treatments contribute to the loss of Ca2+ homeostasis, inhibit glucose uptake, and influence the generation of free radicals but cannot fully explain the decrease in levels of BDNF. Stress may influence the expression of BDNF via regulation of other neurotransmitters, such as the inhibitory neurotransmitter, GABA. Depolarization and increased intracellular Ca2+ mediates the induction of BDNF, probably via the activation of Ca2+/calmodulin kinase (CAMK) and phosphorylation of CREB (cAMP response element binding protein). Activation of GABAA receptors and hyperpolarization of neurons could lead to decreased levels of intracellular Ca2+ and inhibition of BDNF expression. Another possibility is that stress activates some unknown factor(s) that decreases the expression of BDNF via the Ca2+ pathway or via another intracellular pathway and transcription factor. Seizures and mild neuronal insults increase the expression of BDNF and trkB via activation of voltage-sensitive Ca2+ channels (VSCC) and glutamate-gated ionic channels, including glutamate (GLU-R) and NMDA receptors: activation of GLU-R depolarizes neurons via influx of Na+ and allows for activation of NMDA receptors that gate Ca2+ and Na+. Activation of VSCC and NMDA channels increases intracellular Ca2+ that activates the CAMK-CREB pathway leading to expression of BDNF. Under normal conditions, Ca2+ homeostasis is maintained by Ca2+ binding proteins (CBP) and by Ca2+ efflux via an ATP-dependent pump and a Na+/Ca2+ exchanger. Antidepressant treatments increase expression of BDNF and trkB, probably by increasing levels of norepinephrine (NE) and serotonin (5-HT). NE and 5-HT may increase BDNF via activation of receptors that stimulate the cAMP system (e.g., β1-adrenergic [β1AR] and 5-HT4,6,7, respectively). Alternatively, this may occur via receptors that influence Ca2+ kinases (e.g., α1-adrenergic and 5-HT2, not shown). Increased expression of BDNF may contribute to the ability of mild insults and, possibly, antidepressant treatments to protect neurons from stress and neurotoxic insults.

However, the therapeutic action of these treatments is dependent on chronic treatment (several weeks), suggesting that more long-term adaptations to the acute elevation of these monoamines is required. Recent studies demonstrate that neurotrophins selectively increase the function of norepinephrine and serotonin neurons and protect these neurons from neurotoxic damage in adult animals. Thus, decreased expression of neurotrophins could contribute to the loss of monoamine function and the exacerbation of depression, whereas increased expression of neurotrophins could contribute to the therapeutic action of antidepressants via enhanced function of norepinephrine and serotonin neurotransmission.

NT-3 and BDNF have been reported to influence norepinephrine and serotonin neurons. The implantation of fibroblasts that express NT-3, but not other neurotrophins, prevents the degeneration of locus coeruleus neurons in response to the neurotoxin, 6-hydroxydopamine (48). NT-3 or NT-4, but not BDNF or NGF, are reported to increase significantly the survival of embryonic locus coeruleus neurons in culture (32). Chronic infusion of BDNF into the midbrain increases the level of serotonin and its turnover in periaqueductal grey, dorsal, and median raphe, raphe Magnus, and raphe pallidus (49). Local infusion of BDNF into the cerebral cortex increases the density of serotonin immunostaining and protects serotonin neurons from neurotoxin damage (50).
together, the results demonstrate that BDNF and NT-3 increase the growth and survival of norepinephrine and serotonin neurons.

The neurotrophins also increase the survival and function of other neurotransmitter and neuropeptide systems, particularly dopamine and neuropeptide Y, which have been implicated in the pathophysiology and treatment of depression (25). BDNF, NT-3, and NT-4/5 support the survival and development of mesencephalic dopamine neurons and increase the function of mature dopamine neurons in adult rats. BDNF enhances the expression of neuropeptide Y in cultured cortical neurons. Regulation of these and still other neurotransmitter and neuropeptide systems could contribute to a role for neurotrophins in the pathophysiology and treatment of psychiatric illnesses.

**Neurotrophins Exhibit Antidepressant Effects in Behavioral Models**

Enhancement of monoamine function by neurotrophins suggests that these treatments could represent an alternate mechanism to influence behaviors mediated by norepinephrine and serotonin, particularly behavioral models of depression (51). To examine this possibility, the influence of chronic BDNF infusion into the midbrain (near the periaqueductal gray and dorsal raphe) on the forced swim and learned helplessness paradigms was examined. These paradigms have been reported to have validity in predicting drugs with antidepressant activity. In the forced swim test, infusion of BDNF decreased immobility time by approximately 70%, and, in the learned helplessness paradigm, BDNF improved the impairment in the number and latency of attempted escapes to a level comparable to that of control animals. These effects appear to be specific, as BDNF treatment did not significantly influence locomotor activity. The results provide additional support that neurotrophins influence the neurotransmitter systems involved in depression.

**Regulation of Neurotrophins by Antidepressant Treatments**

Electroconvulsive seizure (ECS) therapy is the most effective and rapidly acting treatment for depression and bipolar disorder and is often the last line of treatment for patients who are not responsive to available drug therapies. Seizures induced by electrical stimulation of the hippocampus or pharmacological treatments increase the expression of NGF and BDNF and their receptors in the brain (52, 53). These findings indicate that ECS, and possibly other antidepressant drug treatments, regulate the expression of neurotrophins. This possibility has been examined by determining the influence of ECS and antidepressant drug treatments on the expression of neurotrophins and their receptors.

Acute ECS produces a transient induction of BDNF and trkB mRNA in the hippocampus and cerebral cortex (Fig. 2) (41, 54). In addition, repeated ECS treatment, for the time required to treat depression, enhances the induction of BDNF and trkB in response to acute ECS in the frontal cortex and prolongs the expression of BDNF and trkB in the hippocampus. The enhanced induction and prolonged expression of BDNF and trkB observed after chronic treatment may increase neuronal growth (e.g., by increasing neurite formation) that may contribute to the therapeutic action of this treatment. Such effects may be dependent on the enhanced and prolonged expression of BDNF, as reported in cultured cells (55). This could explain the apparent discrepancy between the acute induction of BDNF and the therapeutic time course of ECS treatment.

The influence of antidepressant drug treatments on the expression of BDNF and trkB has also been examined. Chronic (21 d), but not acute (1 d), treatment with tranylcypromine (21 d), a monoamine oxidase inhibitor antidepressant, significantly increases the expression of BDNF mRNA in the frontal cortex and hippocampus (41, 54). In addition, the chronic administration of sertraline or desipramine, selective serotonin and norepinephrine reuptake inhibitor antidepressants, respectively, tends to increase the levels of BDNF and to increase significantly the levels of trkB in the hippocampus (54). These findings demonstrate that three different classes of antidepressant treatments, as well as ECS treatment, increase the expression of BDNF and/or trkB in the brain, suggesting that this neurotrophin system may be a common target of antidepressant treatments (Fig. 3).

**Influence of Antidepressant Treatments on Cell Atrophy and Survival**

Antidepressant regulation of neurotrophins could reverse the effects of stress on neurotrophin expression and lead to reversal of the stress-induced atrophy of hippocampal neurons. ECS treatment, 2 hours after the initiation of stress, completely reverses the down-regulation of BDNF mRNA in the hippocampus (Morinobu et al., unpublished observations). In addition, administration of a single dose of tranylcypromine or imipramine, a nonselective serotonin and norepinephrine reuptake inhibitor antidepressant, after stress partially blocks the down-regulation of BDNF. The possibility that these effects of antidepressants influence the survival and growth of neurons is supported by a report that the coadministration of tianeptine, an atypical antidepressant, blocks the stress-induced atrophy of CA3 pyramidal neurons (55). Seizures and increased neuronal activity increase cell survival and neurite outgrowth, providing additional evidence that ECS (and possibly antidepressant drugs) may have similar effects (26, 55). Activation of voltage sensitive Ca2+ channels appears to be an important initiating event for increasing neuronal survival (55). Interestingly, activation of voltage sensitive Ca2+ chan-
nels results in a prolonged induction of BDNF (Fig. 3), similar to that observed after chronic ECS, which is required for increased neuronal survival (55). In vivo studies have demonstrated that seizures increase neurite sprouting, particularly in mossy fibers from dentate gyrus granule cells (26); seizures increase the expression of BDNF and trkB in these cells, and BDNF treatment increases axonal sprouting of cultured dentate gyrus granule cells (57). It is notable, as alluded to earlier, that the induction of BDNF in response to seizures (36, 37) parallels the sensitivity of hippocampal neurons to the neurotoxic effects of stress and glucocorticoid treatments: Induction of BDNF is lowest in CA3, where stress- or glucocorticoid-induced atrophy is most prominent.

Focal sprouting, like that induced by stimulating discrete brain regions during kindling or that produced by recurrent epileptic seizures, may underlie increased seizure sensitivity in the affected brain locus. ECS may induce a broader effect on neuronal growth throughout the brain, not just within a specific brain locus, which may have a neuroprotective effect. For example, seizure pretreatment reduces kainic acid-induced cell damage in the hippocampus and piriform cortex (58). One mechanism by which seizures and prolonged BDNF induction may protect neurons is by increasing the expression of calbindin (20, 21), a Ca\(^{2+}\) binding protein that may buffer excess intracellular Ca\(^{2+}\). Another possibility is that neurotrophins protect neurons by reducing oxidative stress (25). In addition, antidepressant treatments, particularly those that increase levels of serotonin, could enhance neurite outgrowth or exhibit neuroprotective effects via regulation of the trophic factor S100 (23).

Based on these findings, it is likely that repeated ECS treatment increases neurite outgrowth and cell survival in the hippocampus and other brain regions. The influence of ECS and other antidepressant treatments on neuronal sprouting and the relevance of sprouting and cell survival to the actions of antidepressant treatments remain to be determined.

**Intracellular Pathways Governing the Expression of BDNF**

Activation of glutamate receptors and voltage-sensitive Ca\(^{2+}\) channels would lead to Ca\(^{2+}\) entry and activation of Ca\(^{2+}\)/calmodulin-dependent protein kinase, which could induce BDNF expression via regulation of transcription factors (Fig. 3). One possible transcription factor is cyclic AMP response element binding protein (CREB), which is activated by Ca\(^{2+}\)/calmodulin-dependent protein kinase as well as by cyclic AMP-dependent protein kinase. In support of this possibility, induction of BDNF in response to glutamate and activation of voltage-sensitive Ca\(^{2+}\) channels has been temporally correlated with phosphorylation of CREB in primary cultures of the cerebral cortex (55). Moreover, a role for CREB in ECS induction of BDNF has been demonstrated using antisense oligonucleotides to decrease expression of CREB in the hippocampus (54). Local infusion of CREB antisense, but not sense, oligonucleotide into the dorsal hippocampus decreases the basal levels of BDNF and blocks the induction of BDNF in response to ECS (Fig. 4). This effect is time dependent and reversible, indicating that CREB antisense treatment does not decrease BDNF expression by damaging the neurons.

A role for CREB and the cAMP system in the expression of BDNF and trkB by antidepressant treatments is further supported by previous studies (47). Antidepressant treatments increase synaptic levels of norepinephrine and serotonin that activate receptors (i.e., β1-adrenergic and 5-HT\(_{4,6,7}\), respectively) coupled to the cAMP system. In addition, other receptors (e.g., α1-adrenergic or 5-HT\(_{2}\)) may be capable of activating calcium kinases. Chronic antidepressant treatments are reported to result in translocation of cAMP-dependent

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**Fig. 4. CREB antisense oligonucleotide decreases the expression of BDNF.** CREB antisense (AS) or sense (S) oligonucleotide infusion into the hippocampus (arrows) mark the site of infusion. Twenty-four hours later, the level of BDNF mRNA was determined after sham or ECS (2 h) treatment by in situ hybridization. CREB antisense, but not sense, oligonucleotide decreased basal and ECS induction of BDNF in the area surrounding the infusion site. Infusion of CREB antisense, but not sense, oligonucleotide decreases the expression of CREB immunohistochemistry (not shown).
protein kinase from the cytosol to the nucleus (59). These findings suggest that the cAMP cascade and expression of BDNF and trkB may be a common target of different classes of antidepressant treatments (Fig. 3).

**Summary and Conclusions**

The studies discussed outline only a fraction of the many and varied effects of stress and adrenal glucocorticoids on neuronal survival and function. Although a complete understanding of these neurochemical and cellular effects will require extensive studies, there are several points worthy of comment. First, stress and glucocorticoid treatments can lead to cell death and atrophy of certain populations of sensitive neurons, whereas other neurons are more resistant. Characterization of the cellular and molecular determinants that make a neuron more sensitive or resistant will enable attempts to prevent or to reverse the deleterious effects of stress. Second, the effects of stress can lead to enhanced toxicity to other types of neuronal insult. Such interactions may explain why stress leads to psychiatric illnesses in some individuals who have been exposed to prior insult or have a genetic predisposition, whereas others, without prior insult, are more resistant. Third, expression of neurotrophins, like BDNF, are rapidly regulated by stress and may thereby contribute to stress-induced cell atrophy and survival. Such acute regulation suggests that neurotrophins may act as modulators of neuronal activity and function and not just as trophic factors. Finally, these effects of stress could underlie, in part, stress-related psychiatric disorders and may be involved in their reversal during treatment. A potential role for cell atrophy and death in certain psychiatric disorders means that these illnesses are not simply a result of neurochemical imbalances of neurotransmitters and their metabolites. Rather, studies of the etiology and treatment of these illnesses must be based on novel hypotheses that involve the cellular and molecular determinants that control the health and survival of neurons.

**References**

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