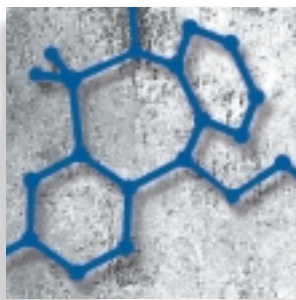


Neural plasticity: consequences of stress and actions of antidepressant treatment

Ronald S. Duman, PhD



Neural plasticity is emerging as a fundamental and critical mechanism of neuronal function, which allows the brain to receive information and make the appropriate adaptive responses to subsequent related stimuli. Elucidation of the molecular and cellular mechanisms underlying neural plasticity is a major goal of neuroscience research, and significant advances have been made in recent years. These mechanisms include regulation of signal transduction and gene expression, and also structural alterations of neuronal spines and processes, and even the birth of new neurons in the adult brain. Altered plasticity could thereby contribute to psychiatric and neurological disorders. This article reviews the literature demonstrating altered plasticity in response to stress, and evidence that chronic antidepressant treatment can reverse or block the effects, and even induce neural plasticity-like responses. Continued elucidation of the mechanisms underlying neural plasticity will lead to novel drug targets that could prove to be effective and rapidly acting therapeutic interventions.

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Neural plasticity is a fundamental process that allows the brain to receive information and form appropriate adaptive responses to the same or similar stimuli. The molecular and cellular adaptations underlying learning and memory are the best-characterized and most-studied examples of neural plasticity. However, many different stimuli can activate neural plasticity processes in different brain structures, including environmental, social, behavioral, and pharmacological stimuli. In fact, it could be argued that neural plasticity is one of the most essential and important processes that the brain performs as it relates to many types of central nervous system functions.

Thus, disrupted or abnormal plasticity could lead to maladaptive neuronal responses and abnormal behavior. This could occur in response to genetic abnormalities of the cellular machinery required for plasticity, and abnormal or inappropriate stimuli. For example, exposure to inappropriate or prolonged stress has been reported to alter molecular and cellular markers of neural plasticity, and could contribute to stress-related mood disorders. This review will discuss the literature demonstrating altered neural plasticity in response to stress, and clinical evidence indicating that altered plasticity occurs in depressed patients. The second part of the review will present evidence that antidepressant treatment blocks the effects of stress or produces plasticity-like responses.

General mechanisms of neural plasticity

Neural plasticity encompasses many different types of molecular and cellular responses that occur when cells in the brain are induced to respond to inputs from other

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Selected abbreviations and acronyms

BDNF	<i>brain-derived neurotrophic factor</i>
cAMP	<i>cyclic adenosine monophosphate</i>
CaRE	<i>cAMP response element</i>
CREB	<i>cAMP response element binding protein</i>
FGF-2	<i>fibroblast growth factor-2</i>
5-HT	<i>5-hydroxytryptamine (serotonin)</i>
LTP	<i>long-term potentiation</i>
NMDA	<i>N-methyl-D-aspartate</i>
PDE4	<i>phosphodiesterase type IV</i>
PKA	<i>protein kinase</i>
SSRI	<i>selective serotonin reuptake inhibitor</i>

cells or circulating factors. The systems that have been most extensively studied are cellular and behavioral models of learning and memory, including long-term potentiation (LTP), in slices of brain and rodent models of behavior. The mechanisms identified for learning and memory most likely also subserve plasticity occurring in other regions and for other adaptive functions of the brain. This section will briefly discuss some general mechanisms and concepts of plasticity.

Mechanisms of acute neural plasticity: synaptic transmission and protein kinases

The effects underlying the rapid responses to neuronal activation are mediated by activation of the excitatory neurotransmitter glutamate and regulation of intracellular signaling cascades (for a review of acute mechanisms underlying LTP, see reference 1). Glutamate causes neuronal depolarization via activation of postsynaptic ionotropic receptors that increase intracellular Na^+ . This leads to the subsequent activation of *N*-methyl-D-aspartate (NMDA) receptors and the resulting influx of Ca^{2+} . Ca^{2+} is a major intracellular signaling molecule that activates a signaling cascade, including activation of Ca^{2+} /calmodulin-dependent protein kinase. Within minutes to hours, activation of glutamate and Ca^{2+} -dependent pathways can result in structural alterations at the level of dendritic spines. Spines mark the location of glutamate synapses and have been the subject of intensive investigation for understanding synaptic plasticity.² Changes in the shape and even number of spines can occur very rapidly (minutes to hours) after glutamate stimulation. These alterations are made permanent or long-term when they are stabilized or consolidated, a process that requires gene expression and protein synthesis.

Mechanisms of long-term plasticity: gene expression and protein synthesis

The Ca^{2+} /cyclic adenosine monophosphate (cAMP) response element (CaRE) binding protein (CREB) is one of the major transcription factors that mediate the actions of Ca^{2+} , as well as cAMP signaling. CREB has been reported to play a role in both cellular and behavioral models of learning and memory.³ There are a number of gene targets that are influenced by Ca^{2+} , cAMP, and CREB, and the pattern of gene regulation is dependent on the cell type, the length of stimulation, as well as the magnitude of stimulation. Gene targets that have been implicated in learning and memory, and are relevant to the effects of stress and antidepressant treatment, are the neurotrophic factors. Of particular interest is brain-derived neurotrophic factor (BDNF), one of the most abundant neurotrophic factors in the brain.

Altered neural plasticity in response to stress

Recent reports have demonstrated altered molecular and cellular responses to stress and have contributed to the hypothesis that altered neural plasticity contributes to stress-related psychiatric illnesses. Some examples of stress responses are discussed in this section.

Stress alters learning and memory

Stress is known to significantly influence learning and memory, and the effects are dependent on the type, duration, and intensity of the stressor. Emotional arousal can enhance learning and memory via synaptic plasticity of amygdala-dependent pathways, and this is thought to be the basis for intense, long-term memories of traumatic events and posttraumatic stress disorder.^{4,5} However, stress can also impair subsequent learning and memory and can even lead to amnesia.⁶ The influence of stress on hippocampal-dependent learning is complex and dependent on the type of learning task.

In studies of LTP, a consistent suppression of neural plasticity is observed after exposure to stress or adrenal glucocorticoids.^{6,7} In one of these studies, the suppression of LTP was observed after exposure to an uncontrollable stressor and correlated with behavioral performance in a learning and memory task. Giving the animals control over the stress (ie, the stress could be terminated) did not lead to reduced LTP or decreased learning and

memory.⁸ A role for BDNF in the actions of stress on LTP has also been suggested.⁹ For additional references and discussion of the effects of stress on learning and memory, see the reviews in references 4 to 7.

Stress causes atrophy of hippocampal neurons

One of the best-characterized examples of altered structural plasticity in response to stress is the atrophy of hip-

pocampal neurons, which was first described by McEwen and colleagues (*Figure 1*).¹⁰ They found that repeated restraint stress results in atrophy of the dendrites of CA3 pyramidal neurons in the hippocampus, measured as a decrease in the number and length of apical dendrites.¹¹ The reduction in dendritic arborization was found to be dependent on long-term, repeated exposure to restraint stress (3 weeks) and to be reversible when the animals are removed from stress. The atrophy

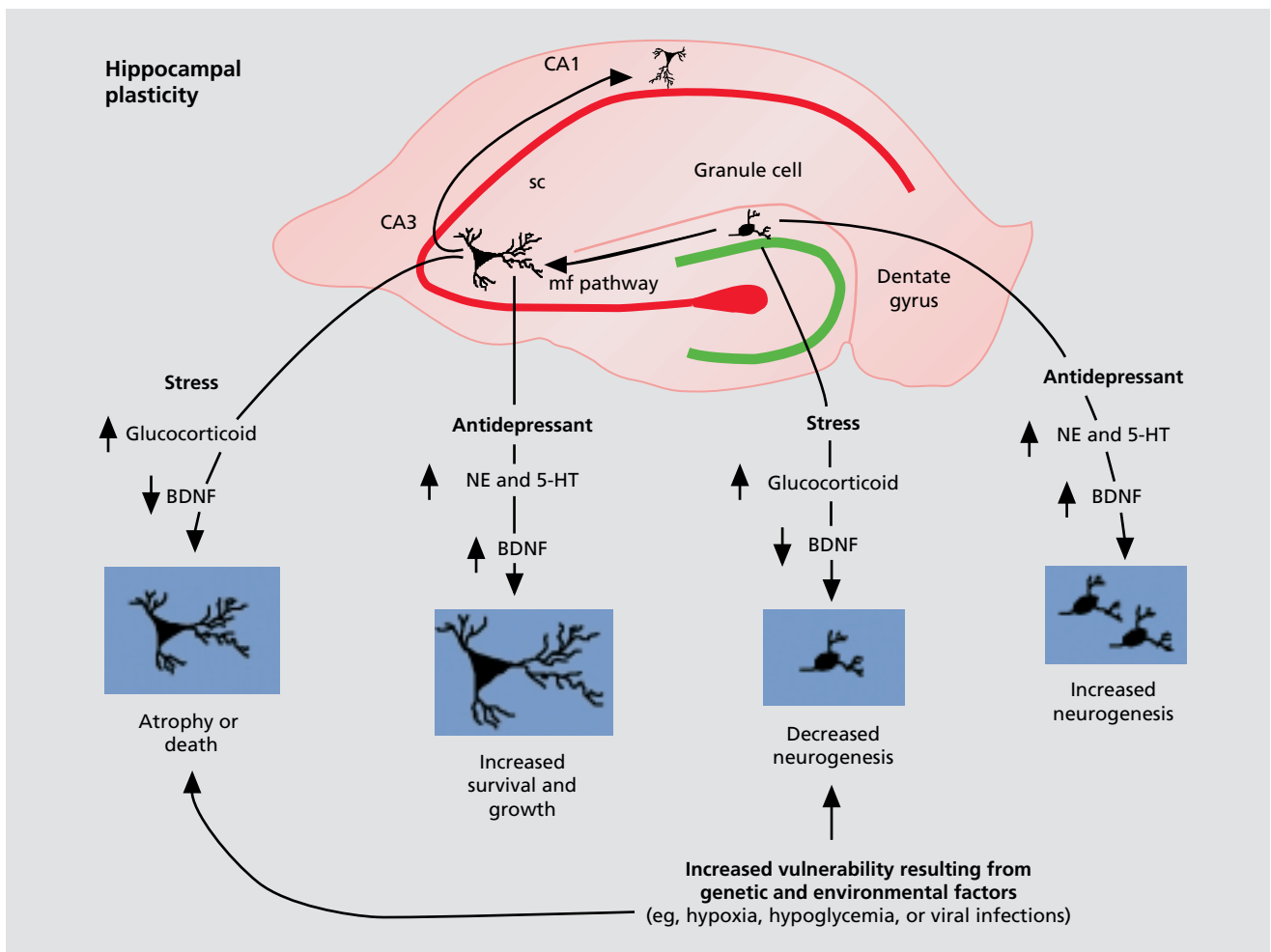


Figure 1. Model of hippocampal plasticity showing structural alterations in response to stress: atrophy of CA3 pyramidal neurons and decreased neurogenesis of dentate gyrus granule cells. Stress results in powerful effects on the hippocampus, partly because of the high levels of glucocorticoid receptors expressed in this brain region. Stress results in at least two major actions in two different subfields of the hippocampus. Repeated stress causes atrophy or remodeling of CA3 pyramidal neurons, decreasing the number and length of apical dendrites. Administration of glucocorticoids causes a similar effect, and decreased expression of brain-derived neurotrophic factor (BDNF) could contribute to pyramidal cell atrophy. Stress also decreases the proliferation of newborn granule cells in the dentate gyrus, and glucocorticoid administration mimics this effect. Chronic antidepressant administration can reverse the atrophy of CA3 neurons and block the downregulation of neurogenesis in the dentate gyrus. The effects of antidepressant treatment occur via acute regulation of serotonin (5-hydroxytryptamine [5-HT]) and norepinephrine (NE) and the regulation of intracellular signaling and gene expression. mf, mossy fiber; sc, Schaffer collaterals.

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of CA3 pyramidal cells appears to result from the elevation of adrenal glucocorticoids that occurs during stress because chronic administration of corticosterone, the active form in rodent, results in a similar decrease in number and length of dendrites.¹² The actions of stress and glucocorticoids are blocked by administration of an NMDA receptor antagonist, indicating that this glutamate receptor is required for atrophy of CA3 neurons.¹⁰ Atrophy of CA3 pyramidal neurons occurs after 2 to 3 weeks of exposure to restraint stress or more long-term social stress, and has been observed in rodents and tree shrews.¹¹⁻¹³ In contrast to the atrophy of hippocampus, recent studies demonstrate that chronic stress causes hypertrophy of neurons in the amygdala.¹⁴ This study found chronic immobilization stress increased the dendritic arborization of pyramidal neurons in the basolateral amygdala, but decreased dendrite length and branching in the CA3 pyramidal neurons of the hippocampus. Hypertrophy of the amygdala could underlie increased learning and memory as a result of stress-induced emotional arousal, and may be relevant to the pathophysiology of stress-related disorders, including anxiety, posttraumatic stress, and depression. Increased

arborization of neurons in the amygdala could thereby enhance emotional states or disrupt normal processing of emotional responses.

Stress decreases neurogenesis in the adult hippocampus

In addition to regulation of the morphology of neurons in the hippocampus, stress influences the number of newborn neurons or neurogenesis in the adult hippocampus^{15,16} (Figures 1 and 2). The hippocampus is one of two brain regions where neurogenesis continues to occur in adult organism (the other region is in the subventricular zone). In the hippocampus, neural progenitor cells are found in the subgranular zone, between the granule cell layer and the hilus. These cells give rise to newborn cells that migrate into the granule cell layer and mature into neurons with the morphological and physiological characteristics of adult granule cells.¹⁷ Interestingly, the process of neurogenesis is highly regulated by a variety of stimuli and can be considered a form of neural plasticity. For example, enriched environment, exercise, and learning increase neurogenesis, while aging and exposure to drugs of abuse decrease neurogenesis.^{15,16,18}

In addition to these factors, stress also results in a dramatic downregulation of neurogenesis in the hippocampus.^{10,18} Exposure to just a single stressor is sufficient to significantly decrease neurogenesis in the adult hippocampus. Adult neurogenesis is decreased by different types of stress, including subordination stress,¹⁹ predator odor,²⁰ maternal separation,²¹ and footshock.²² In addition, exposure to inescapable stress in the learned helplessness model of depression decreases adult neurogenesis and this effect correlates with behavioral despair in this model.²² Moreover, the reduction in neurogenesis and the behavioral despair is reversed by antidepressant treatment.

Regulation of CREB and decreased expression of BDNF in response to stress

Stress results in a wide range of effects that influence many different neurotransmitter and neuropeptide systems, signal transduction pathways, and altered gene expression. The hallmark of the stress response is activation of the hypothalamic-pituitary-adrenal (HPA) axis, which includes increased circulating levels of

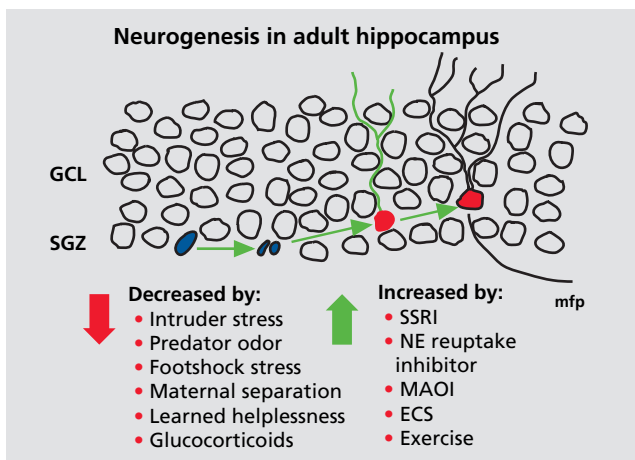


Figure 2. Model demonstrating the regulation of adult neurogenesis in the hippocampus. Neural progenitor cells are restricted to the subgranular zone (SGZ) that is located between the granule cell layer (GCL) and hilus. These progenitor cells give rise to newborn neurons that migrate into the granule cell layer and mature into adult neurons. The proliferation and survival of newborn neurons is subject to change and can be considered a form of neural plasticity. Neurogenesis is influenced by a number of different stimuli in either a positive or a negative manner as indicated. SSRI, selective serotonin reuptake inhibitor; NE, norepinephrine; MAOI, monoamine oxidase inhibitor; ECS, electroconvulsive seizures; mfp, mossy fiber pathway.

adrenal glucocorticoids. The hippocampus contains very high levels of glucocorticoid receptors and is therefore significantly impacted by stress. As mentioned above, studies by McEwen and colleagues have demonstrated that glucocorticoids contribute to the atrophy and decreased neurogenesis of hippocampal neurons resulting from exposure to stress.¹⁰

In addition, stress is reported to influence CREB and BDNF in the hippocampus and other brain regions. The transcriptional activity of CREB is regulated by phosphorylation and levels of phospho-CREB are used as an indirect measure of CREB activation and function (Figure 3). The regulation of phospho-CREB is complex and is dependent on the brain region and whether the stress is acute or chronic.²³⁻²⁶ Acute stress increases levels of phospho-CREB in many limbic regions associated with mood disorders and this may represent a normal or appropriate adaptive responsiveness.²⁴ In contrast, chronic stress leads to decreased levels of phospho-CREB in many limbic brain regions, which could lead to decreased plasticity and function.²⁶

Stress has profound effects on the expression of BDNF in the hippocampus. Levels of BDNF expression in hippocampus are dramatically downregulated by both acute and chronic stress, and this effect could contribute to the atrophy and decreased neurogenesis caused by stress (Figure 1).²⁷⁻²⁹ The role of other factors that could underlie the actions of stress on adult neurogenesis is a subject of interest and could lead to novel targets for drug development.

Atrophy of limbic brain structures in depressed patients

Evidence from basic research studies provide strong support for the hypothesis that stress-related illnesses such as depression could include alterations in brain structure and neural plasticity. Indeed, direct evidence to support this hypothesis has been provided by brain imaging and postmortem studies of depressed patients.

Evidence from brain imaging studies

Magnetic resonance imaging studies have demonstrated that the size of certain brain structures is decreased in mood disorder patients. In particular, these studies demonstrate that the volume of the hippocampus is decreased in patients with depression.^{30,31} Reduced hip-

pocampal volume is also observed in patients with post-traumatic stress disorder (PTSD).³² The reduction in hippocampal volume is directly related to the length of illness.^{33,34} In addition to hippocampus, atrophy of prefrontal cortex and amygdala—brain regions that control cognition, mood, and anxiety—has also been reported in patients with depression or bipolar disorder.³⁵

Evidence from postmortem studies

Atrophy of hippocampus or other brain regions could result from loss of cells (neurons or glia) or decreased size of the cell body or neuronal processes. The most extensive studies have been conducted on prefrontal and cingulate cortex and demonstrate that the neuronal body size and number of glia is decreased in depressed patients.³⁶⁻³⁸ There is much less known about the hippocampus and additional studies will be required to determine what accounts for the atrophy of hippocampus observed in depressed patients.

Postmortem analysis of CREB and BDNF has also provided evidence consistent with a loss of neural plasticity in depression. Levels of CREB are decreased in the cerebral cortex of depressed patients or suicide victims.^{39,40} Levels of BDNF are also decreased in prefrontal cortex and hippocampus of depressed patients.⁴¹ Reduced levels of CREB and BDNF, two molecular markers of neural plasticity, indicate that the ability of limbic brain structures to mount adaptive responses is compromised in depressed patients.

Antidepressant treatment increases neural plasticity

In contrast to the effects of stress, antidepressant treatment results in molecular and cellular responses that demonstrate an increase in neural plasticity. Moreover, these studies have paved the way for additional studies that demonstrate that antidepressant treatment results in structural remodeling. In many cases, the effects of antidepressant treatment oppose or reverse the effects of stress. Taken together, these findings provide additional support for the hypothesis that neural plasticity plays a significant role in the treatment, as well as the pathophysiology of mood disorders. The evidence for regulation of neural plasticity at the level of neurogenesis, signal transduction, and gene expression is discussed in the second half of this review.

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Antidepressant treatment increases adult neurogenesis

Neurogenesis is increased by chronic antidepressant administration

One of the most surprising discoveries of recent times in the field of depression is that antidepressant treatment regulates neurogenesis in the adult hippocampus (*Figures 1 and 2*). In contrast to the actions of stress, chronic antidepressant treatment increases the number of newborn neurons in the adult hippocampus of rodents or tree shrews.^{42,43} The upregulation of neurogenesis is dependent on chronic antidepressant treatment, consistent with the time course for the therapeutic action of antidepressants.⁴³ In addition, different classes of antidepressants, including serotonin (5-hydroxytryptamine [5-HT]) and noradrenaline reuptake inhibitors, and electroconvulsive seizures are reported to increase adult neurogenesis.⁴³⁻⁴⁵ Antidepressant treatment influences two important aspects of neurogenesis, the rate of cell proliferation (ie, the number of newborn neurons) and the survival of newborn neurons.⁴⁶ An increase in the number of newborn neurons could contribute to the reversal of hippocampal atrophy observed in depressed patients.

Antidepressant treatment blocks the downregulation of neurogenesis caused by stress

The influence of antidepressant treatment in the context of stress has also been examined. These studies demonstrate that chronic antidepressant treatment can block or reverse the downregulation of neurogenesis that results from exposure to stress. Several different types of stress have been tested, including blockade of intruder stress,⁴² maternal separation,⁴⁷ and learned helplessness.²² In addition, different types of antidepressants have been tested, including an atypical antidepressant, tianeptine,⁴² a selective serotonin reuptake inhibitor (SSRI),^{22,47} and a neurokinin-1 receptor antagonist.⁴⁸ The influence of antidepressant treatment on the atrophy of CA3 pyramidal neurons resulting from chronic exposure to stress has been examined. These studies demonstrate that chronic administration of tianeptine blocks the atrophy of CA3 apical dendrites that is caused by stress.¹² Chronic administration of an SSRI antidepressant did not block the atrophy of CA3 neurons in this study. Analysis of dendrite branch number and length is tedious and

labor intensive, but additional studies of other antidepressants are necessary to determine the relevance of this effect in the actions of antidepressant treatment.

A functional role for neurogenesis in the action of antidepressant treatment

A major issue in the field of adult neurogenesis is how to test the function of newborn neurons. A recent study has addressed this question by using a combination of irradiation and mutant mouse approaches.⁴⁹ This study demonstrates that focused irradiation of hippocampus in the mouse completely blocks neurogenesis and there was a corresponding blockade of the behavioral actions of antidepressant treatment in two behavioral models, novelty suppressed feeding and chronic mild stress. In addition, Santarelli et al⁴⁹ studied the effects of antidepressants in mice with a null mutation of the 5-HT_{1A} receptor, a subtype that has been implicated in the actions of antidepressant treatment. They found that upregulation of neurogenesis by chronic administration of an SSRI was completely blocked in 5-HT_{1A} null mutant mice, and that the behavioral effects of SSRI treatment were similarly blocked. These results are the first evidence that increased neurogenesis is necessary for an antidepressant response in behavioral models. There are a few limitations to this study. First, although novelty-suppressed feeding is responsive to chronic antidepressant treatment—and this is why it was chosen—this paradigm is a better model of anxiety than depression. Second, although the effects of antidepressant treatment were blocked, irradiation and 5-HT_{1A} null mutation alone, in the absence of antidepressant administration, did not produce a depressive phenotype. This is consistent with another report demonstrating that decreased neurogenesis is not correlated with behavior in the learned helplessness model of depression.⁵⁰ Together these studies indicate that neurogenesis is not required for baseline response. However, it is possible that intact neurons are sufficient to sustain baseline response and that more long-term inhibition of neurogenesis would be required to influence activity.

The cAMP-CREB cascade and depression

Neural plasticity upon antidepressant treatment is likely to involve adaptations of multiple intracellular signaling cascades and even interactions of these pathways. One

of the pathways that is regulated by antidepressant treatment and has been demonstrated to contribute to the actions of chronic antidepressant responses is the cAMP-CREB cascade, the subject of this section. However, it is likely that other signaling pathways are also regulated by—and play a role in—the actions of antidepressants. For reviews covering other signal transduction pathways, see reference 51 and 52.

Antidepressant treatment upregulates the cAMP-CREB cascade

Several studies have investigated the influence of antidepressant treatment on the cAMP-CREB pathway (Figure 3).^{53,54} This work demonstrates that chronic antidepressant treatment upregulates the cAMP second-messenger cascade at several different levels. This includes

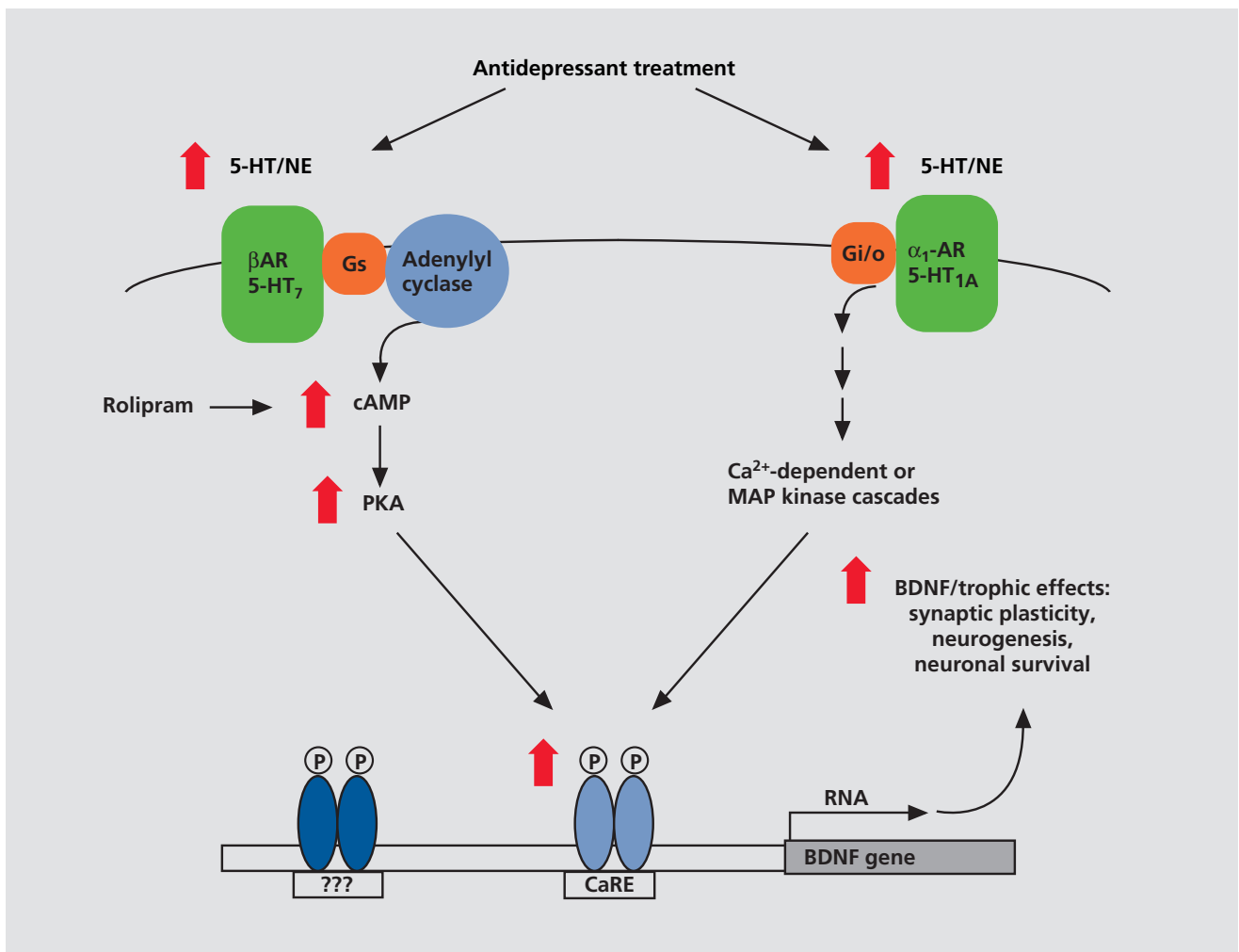


Figure 3. Model demonstrating the upregulation of the cyclic adenosine monophosphate (cAMP)–cAMP response element binding protein (CREB) cascade and expression of brain-derived neurotrophic factor (BDNF) by antidepressant treatment. Chronic, but not acute, antidepressant treatment upregulates the cAMP-CREB cascade in limbic regions of the brain including the hippocampus and cerebral cortex. This includes increased coupling of stimulatory G protein (Gs) to adenylyl cyclase, increased levels of cAMP-dependent protein kinase (PKA), and increased function and expression of CREB. CREB can also be phosphorylated and activated by other kinases, including Ca²⁺/calmodulin-dependent kinase and mitogen-activated protein (MAP) kinase. In this way, CREB could serve as a common target for different types of serotonin (5-hydroxytryptamine [5-HT]) and norepinephrine (NE) receptors, including β-adrenergic (βAR), 5-HT₇, α₁-adrenergic (α₁AR), and 5-HT_{1A} receptor subtypes. One downstream target of CREB that has been shown to have antidepressant effects is BDNF. The BDNF promoter has at least one Ca²⁺/cAMP response element (CaRE) that is regulated by phosphorylation (P) of CREB.

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increased coupling of the stimulatory G protein to adenylyl cyclase, increased levels of cAMP-dependent protein kinase (PKA), and increased levels of CREB as well as phospho-CREB.⁵⁵⁻⁵⁷ Upregulation of these components of the cAMP-CREB signaling pathway is dependent on chronic antidepressant treatment, consistent with the time course for the therapeutic action of antidepressants. In addition, upregulation of the cAMP-CREB cascade is observed in response to chronic administration of different classes of antidepressants, indicating that this is a common target of antidepressant treatment.

In addition to phosphorylation by PKA, CREB is also phosphorylated by Ca²⁺-dependent protein kinases, such as Ca²⁺/calmodulin-dependent protein kinase, and by mitogen-activated protein kinase pathways (*Figure 3*). In this way, CREB can serve as a target for multiple signal transduction pathways and neurotransmitter receptors that activate these cascades.

Activation of the cAMP-CREB cascade produces an antidepressant response

Direct evidence for cAMP-CREB signaling in the action of antidepressant treatment has been tested by pharmacological, viral vector, and mutant mouse approaches. First, drugs that block the breakdown of cAMP produce an antidepressant response in behavioral models of depression.⁵⁴ The primary target for inhibition of cAMP breakdown is cAMP-specific phosphodiesterase type IV (PDE4), and rolipram was one of the first selective PDE4 inhibitors. In addition, we have found that chronic rolipram administration increases neurogenesis in adult hippocampus.^{46,58}

Second, viral expression of CREB in the hippocampus of rat produces an antidepressant response in the forced swim and learned helplessness models of depression.⁵⁹ However, further studies demonstrated that the effects of CREB are dependent on the brain region where it is expressed. For example, expression of CREB in the nucleus accumbens produces a prodepressant effect, while expression of a dominant negative mutant of CREB results in an antidepressant response in the forced swim test.⁶⁰ Transgenic expression of dominant negative CREB in the nucleus accumbens is consistent with this effect.⁶¹ The different behavioral effects of CREB can be explained by different target genes in the hippocampus (ie, BDNF) versus the nucleus accumbens (ie, prodynorphin).

Regulation of neurotrophic factors and depression

The regulation of CREB by antidepressant treatment indicates that regulation of gene expression also plays a role in the actions of antidepressants. There have been many gene targets identified for antidepressants,^{51,52} but BDNF is one that has gained attention and is relevant to neural plasticity responses to antidepressant medications. Studies to identify additional gene targets and gene profiles using gene microarray analysis are currently being conducted.

Antidepressant treatment upregulates BDNF

Neurotrophic factors were originally identified and studied for their role in development and neuronal survival. However, it is now clear that these factors are expressed in the adult brain, are dynamically regulated by neuronal activity, and are critical for the survival and function of adult neurons. On the basis of these considerations, it is clear why decreased expression of BDNF could have serious consequences for the function of limbic brain structures that control mood and cognition. In contrast, antidepressant treatment results in significant upregulation of BDNF in the hippocampus and cerebral cortex of rodents.^{28,53,54} Increased expression of BDNF is dependent on chronic treatment, and is observed with different classes of antidepressants, but not other psychotropic drugs. The induction of BDNF would be expected to protect neurons from damage resulting from stress, elevated glucocorticoids, or other types of neuronal insult.

BDNF has antidepressant effects in behavioral models of depression

The possibility that BDNF contributes to the actions of antidepressant treatment is supported by behavioral studies of recombinant BDNF and transgenic mouse models. Microinfusions of BDNF into the hippocampus produce an antidepressant-like response in the learned helplessness and forced swim models of depression.⁶² The antidepressant effect of BDNF is observed after a single infusion, compared with repeated administration of a chemical antidepressant, and is relatively long-lasting (up to 10 days after infusion). Transgenic overexpression of a dominant negative mutant of the BDNF receptor, trkB, in the hippocampus and other forebrain

structures is also reported to block the effect of antidepressant treatment, demonstrating that BDNF signaling is necessary for an antidepressant response.⁶³

Microinfusions of BDNF into the dorsal raphe, a mid-brain region where 5-HT cell bodies are localized, also produces an antidepressant response in the learned helplessness model.⁶⁴ Together, these studies indicate that BDNF could contribute to antidepressant responses in both forebrain and brain stem structures by affecting different populations of neurons. Alternatively, it is possible that microinfusions of BDNF into the hippocampus influence 5-HT neuronal function by acting at presynaptic sites, and could therefore enhance 5-HT signaling as observed after brain stem infusions of BDNF.⁶⁴

A neurotrophic hypothesis of depression

Basic research and clinical studies of BDNF have resulted in a neurotrophic hypothesis of depression and antidepressant action.^{53,54} This hypothesis is based in part on studies demonstrating that stress decreases BDNF, reduces neurogenesis, and causes atrophy or CA3 pyramidal neurons. Brain imaging and postmortem studies provide additional support, demonstrating atrophy and cell loss of limbic structures, including the hippocampus, prefrontal cortex, and amygdala. In contrast, antidepressant treatment opposes these effects of stress and depression, increasing levels of BDNF, increasing neurogenesis, and reversing or blocking the atrophy and cell loss caused by stress and depression. Additional brain imaging and postmortem studies, as well as basic research approaches will be required to further test this hypothesis. In any case, the studies to date provide compelling evidence that neural plasticity is a critical factor in the pathophysiology and treatment of depression.

Antidepressants influence other neurotrophic factor systems

Because of the preclinical and clinical evidence implicating neurotrophic factors in the pathophysiology and treatment of depression, studies have been conducted to examine other neurotrophic factor systems. One of the most robust effects identified to date is that antidepressant treatment increases the expression of fibroblast growth factor-2 (FGF-2).⁶⁵ FGF-2 is known to have a potent influence on neurogenesis during development and in the adult brain, and could contribute to antide-

pressant regulation of neurogenesis. Studies are under way to examine the role of FGF-2 in antidepressant regulation of neurogenesis and regulation of behavior in models of depression. Several other growth factors have been identified by microarray analysis and gene expression profiling, including vascular endothelial growth factor, neuritin, and VGF.⁶⁶ Studies are currently under way to determine the functional significance of these growth factors in models of depression.

Clinical evidence of relevance of neural plasticity to antidepressant treatment

Basic research studies clearly demonstrate that antidepressant treatment regulates signal transduction, gene expression, and the cellular responses that represent neural plasticity. This issue is more difficult to address in clinical studies, but evidence is slowly accumulating. Brain imaging studies have been conducted to examine the influence of antidepressants on the volume of limbic brain regions. One study demonstrates that hippocampal atrophy is inversely proportional to the length of time a patient receives antidepressant medication.⁶⁷ A longitudinal study of PTSD patients before and after antidepressant treatment has found that there is a partial reversal of hippocampal atrophy in patients receiving medication.⁶⁸ The latter study demonstrated a corresponding increase in verbal declarative memory in response to antidepressant treatment.

Evidence at the molecular level is also provided by postmortem studies. Levels of CREB immunoreactivity are increased in patients receiving antidepressant treatment at the time of death relative to unmedicated patients.³⁹ In addition, levels of BDNF are increased in patients taking an antidepressant at the time of death.⁵⁹ Although these effects must be replicated and extended (for example, to the regulation of neurogenesis) in additional banks of postmortem tissue, the results are consistent with the hypothesis that neural plasticity is upregulated in patients receiving antidepressant medication.

Novel targets for the treatment of depression

The hypothesis that antidepressant treatment increases neural plasticity provides a number of novel targets for drug development. However, as with any fundamentally important mechanism, care must be taken that the drugs developed for such targets do not interfere with the nor-

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mal function of the brain. Nevertheless, regulation of neural plasticity is an exciting area of research for design of new drugs for a variety of indications, including learning, memory, cognition, mood, and neurodegenerative disorders. This section discusses a few of these targets in the context of the pathways regulated by antidepressants and stress.

Targets for antidepressant regulation of neurogenesis

Identification of the signal transduction and gene expression pathways that are responsible for the actions of antidepressant regulation of neurogenesis is a subject of intense investigation. Activation of the cAMP-CREB signaling cascade using either pharmacological or transgenic approaches is reported to increase both proliferation and survival of newborn neurons in the hippocampus,^{46,58} supporting the possibility that antidepressants increase neurogenesis via regulation of this intracellular pathway. Gene targets of CREB, as well as other neurotrophic/growth factors that have been shown to regulate adult neurogenesis, include BDNF, FGF-2, and insulin-like growth factor-1, to name but a few.¹⁸ Because antidepressant treatment increases the expression of both BDNF and FGF-2, these two factors are currently being investigated. This is just a partial listing of the signal transduction cascades and factors that could contribute to antidepressant regulation of adult neurogenesis.

Targets for regulation of the cAMP-CREB cascade

There are several different sites within the cAMP pathway that could be targeted for drug development. One that has already proven to be effective for antidepressant treatment is blockade of PDE4 and the breakdown of cAMP. Rolipram is a PDE4-selective inhibitor that has been demonstrated to have antidepressant efficacy in early clinical trials and behavioral models of depression.^{69,70} However, the clinical use of rolipram has been limited by its side effects, primarily nausea.

The identification of four different PDE4 isozymes that are equally inhibited by rolipram raises the possibility that one of the isozymes underlies the antidepressant actions of rolipram, while another mediates its side effects. Studies are currently under way to characterize the regional distribution and function of the three PDE4 isozymes expressed in brain (PDE4A, PDE4B, and PDE4D) and the role of these isozymes in the actions of

antidepressant treatment.⁷¹ Studies of mutant mice demonstrate that null mutation of PDE4D produces an antidepressant-like phenotype indicating a role for this isozyme,⁷² and similar studies are currently under way for PDE4A and PDE4B.

BDNF as a target for drug development

The use of BDNF and other neurotrophic factors for the treatment of neurological disorders has been a subject of interest for several years, although problems with delivery, efficacy, and side effects have hampered these efforts. To more directly replicate the *in vivo* situation, it may be possible to stimulate the expression of endogenous BDNF expression by stimulating signaling pathways known to regulate this neurotrophic factor. First, activation of the cAMP-CREB cascade by inhibition of PDE4 increases the expression of BDNF.⁵⁶

Small molecular agonists for neurotransmitter receptors have also exhibited some promise. Activation of ionotropic glutamate receptors increases BDNF expression and could be targeted for the treatment of depression.⁷³ One drug that modulates glutamate transmission and increases BDNF expression is memantine.⁷⁴ Riluzole, a sodium channel blocker, also increases BDNF expression, as well as neurogenesis in adult hippocampus.⁷⁵ Specific 5-HT and norepinephrine receptor subtypes that activate cAMP (eg, β -adrenergic, 5-HT₇), Ca²⁺, or mitogen-activated protein kinase (α_1 -adrenergic, 5-HT_{1A}) pathways could also be targets for development. Characterization of the antidepressant actions of these compounds will be needed, as well as identification of additional neurotransmitter and signal transduction systems that regulate BDNF.

Conclusions

Studies of the molecular and cellular mechanisms underlying neural plasticity responses in learning and memory, as well as fear, anxiety, depression, and drug abuse to name but a few, are some of the most exciting and rapidly advancing areas of research in neuroscience. Progress in our understanding of neural plasticity has profound implications for the treatment of a number of psychiatric and neurodegenerative disorders, and for enhancing performance in what are considered normal subjects. One of the promising aspects of neural plasticity is that it implies that the alterations that occur are

reversible, even neuronal atrophy and cell loss. Reversibility of structural as well as functional plasticity has already been demonstrated in response to pharmacological treatments or even behavioral therapy. As the fundamental mechanisms of neural plasticity are further elucidated, new targets and paradigms for enhancing

plasticity will be revealed and will lead to more effective and faster-acting therapeutic interventions. □

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Plasticidad neuronal: consecuencias del estrés y efectos del tratamiento antidepresivo

La plasticidad neuronal está resultando un mecanismo fundamental y específico de la función neuronal, lo que permite que el cerebro reciba información y ejecute las respuestas de adaptación apropiadas a los estímulos correspondientes. El esclarecimiento de los mecanismos moleculares y celulares que subyacen a la plasticidad neuronal es uno de los objetivos principales de la investigación en neurociencias y se han realizado avances significativos en esta área en los últimos años. Estos mecanismos incluyen la regulación de la transducción de señales y la expresión génica, como también las alteraciones estructurales de las espinas neuronales y sus procesos e incluso el nacimiento de nuevas neuronas en el cerebro adulto. La alteración de la plasticidad podría participar en los trastornos psiquiátricos y neurológicos. Este artículo revisa la literatura que demuestra que hay una modificación en la respuesta de estrés y hay evidencias que el tratamiento antidepresivo crónico puede revertir o bloquear estos efectos, e incluso inducir respuestas neurales semejantes a la plasticidad. El esclarecimiento continuo de los mecanismos que subyacen a la plasticidad neuronal conducirá a blancos para nuevos fármacos que podrían llegar a constituirse en intervenciones terapéuticas efectivas y de rápida acción.

Neuroplasticité : conséquence du stress et actions des traitements antidépresseurs

La neuroplasticité se révèle être un mécanisme fondamentale et déterminant de la fonction neuronale, permettant au cerveau de recevoir l'information et d'apporter les réponses adaptatives appropriées aux stimuli ultérieurs qui s'y rattachent. L'élucidation des mécanismes moléculaires et cellulaires sous-jacents à la neuroplasticité est un objectif majeur de la recherche en neurosciences et des progrès significatifs ont été réalisés ces dernières années. Ces mécanismes comprennent la régulation de la transduction du signal et de l'expression du gène ainsi que les altérations structurales des prolongements et des épines dendritiques des neurones et même la naissance de nouveaux neurones dans le cerveau adulte. L'altération de ces mécanismes pourrait contribuer aux pathologies psychiatriques et neurologiques. Cet article passe en revue la littérature pour faire le point sur les arguments en faveur de l'altération de la plasticité en réponse au stress et de la capacité du traitement antidépresseur au long cours à inverser ou neutraliser les effets voire même à susciter des réponses semblables à celles de la neuroplasticité. La poursuite des efforts pour élucider les mécanismes sous-jacents à la neuroplasticité permettra de définir de nouvelles cibles médicamenteuses et de déboucher ainsi sur des interventions thérapeutiques efficaces et d'action rapide.

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