

Neuronal damage and protection in the pathophysiology and treatment of psychiatric illness: stress and depression

Ronald S. Duman, PhD



The discovery that stress and depression, as well as other psychiatric illnesses, are characterized by structural alterations, and that these changes result from atrophy and loss of neurons and glia in specific limbic regions and circuits, has contributed to a fundamental change in our understanding of these illnesses. These structural changes are accompanied by dysregulation of neuroprotective and neurotrophic signaling mechanisms that are required for the maturation, growth, and survival of neurons and glia. Conversely, behavioral and therapeutic interventions can reverse these structural alterations by stimulating neuroprotective and neurotrophic pathways and by blocking the damaging, excitotoxic, and inflammatory effects of stress. Lifetime exposure to cellular and environmental stressors and interactions with genetic factors contribute to individual susceptibility or resilience. This exciting area of research holds promise and potential for further elucidating the pathophysiology of psychiatric illness and for development of novel therapeutic interventions.

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Author affiliations: Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut, USA

A role for damage and protection of neurons in the pathophysiology and treatment of psychiatric illness, including major depressive disorder (MDD) is based on molecular, cellular, and morphological studies in experimental animals and in human patients. Preclinical studies demonstrate that chronic stress causes alterations to the number and shape of neurons and glia in brain regions implicated in mood disorders.¹⁻⁴ Advances in human brain imaging have also reported decreased volumes of limbic brain regions implicated in depression.^{5,6} Preclinical and postmortem studies of signal transduction pathways and target genes have extended this work at the molecular level, demonstrating dysregulation of neurotrophic factors and neuroprotective mechanisms in response to stress and in depressed patients.^{1,2,7} Conversely, chronic administration of therapeutic agents blocks the effects of stress or leads to induction of neurotrophic and neuroprotective pathways.^{2,8} Together, these findings have contributed to a fundamental shift in our understanding of the cause and treatment of psychiatric illnesses and the role of neurotrophic and neuroprotective mechanisms.

This review will present evidence demonstrating neuronal damage, atrophy, and cell loss in response to stress and depression, and the mechanisms underlying these effects. Studies demonstrating the neuroprotective actions of therapeutic agents that counteract the effects of stress and depression will also be discussed. Related aspects of this work are the effects of environment, cellular stressors, insults, and interactions with genetic factors that increase susceptibility and thereby cause dam-

Address for correspondence: Department of Psychiatry, Yale University School of Medicine, 34 Park Street, 3rd floor, New Haven, CT 06508, USA (e-mail: ronald.duman@yale.edu)

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Selected abbreviations and acronyms

ADT	<i>antidepressant treatment</i>
AMPA	<i>α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionic acid</i>
BDNF	<i>brain derived neurotrophic factor</i>
IDO	<i>indoleamine 2,3-dioxygenase</i>
MDD	<i>major depressive disorder</i>
NMDA	<i>N-methyl-D-aspartic acid</i>
PFC	<i>prefrontal cortex</i>
TNF	<i>tumor necrosis factor</i>

age and illness (Figure 1). Conversely, life history of behavior or therapies that reduce stress and enhance neuronal survival, such as exercise, diet, medications, and interactions with genetic factors that increase resilience are neuroprotective, and reverse or block the damaging effects of stress.

In addition, cellular growth and survival are intimately controlled by neuronal activity (Figure 1). This is due to the activity-dependent requirement for expression of neurotrophic factors and other survival pathways and mechanisms that control neurotransmission and neuroplasticity, as well as proliferation, growth, and survival.

Structural/cellular alterations in mood disorders

Depression, like most other major psychiatric illnesses, is widely accepted to be caused by neurochemical imbalances in regions of the brain that are known to control mood, anxiety, cognition, and fear. These regions include the hippocampus, prefrontal cortex (PFC), cingulate cortex, nucleus accumbens, and amygdala. In addition, brain imaging and postmortem studies have identified structural alterations in MDD patients that indicate reductions in dendrite arborization and complexity, and decreased numbers of neurons and glia in these brain regions, all of which could contribute to depressive symptoms (Figure 2). Together, these findings provide compelling evidence for disruption of neurotrophic factors and neuroprotective mechanisms in the pathophysiology of depression.

Structural alterations

One of the regions of interest in depression, as well as other disorders, is the hippocampus, a structure that contains high levels of receptors for glucocorticoids. Imaging

studies have consistently reported that the volume of the hippocampus is decreased 10% to 20% in MDD patients.^{9-12,13,14} There is also evidence of a negative correlation with the length of illness and reversal with antidepressant treatment (ADT),¹⁵ but additional studies are needed to further examine these relationships and to determine whether the reduction is a result or a cause of depressive illness. It is also notable that hippocampal volume reductions have been reported in other stress-related illnesses, including post-traumatic stress disorder (PTSD)^{16,17} and schizophrenic patients.¹⁸

The PFC is another “stress-responsive” brain region implicated in depression. The primary function of the PFC is cognition, working memory, and inhibitory control of brain regions that underlie fear and emotion. Brain imaging studies have reported a significant reduction in the volume of the PFC in MDD patients, which could underlie the reported hypofunction of this structure, most notably decreased cognition.^{9,15,19,20}

Cellular alterations

Different types of cellular alterations could account for the volume reductions observed in the hippocampus,

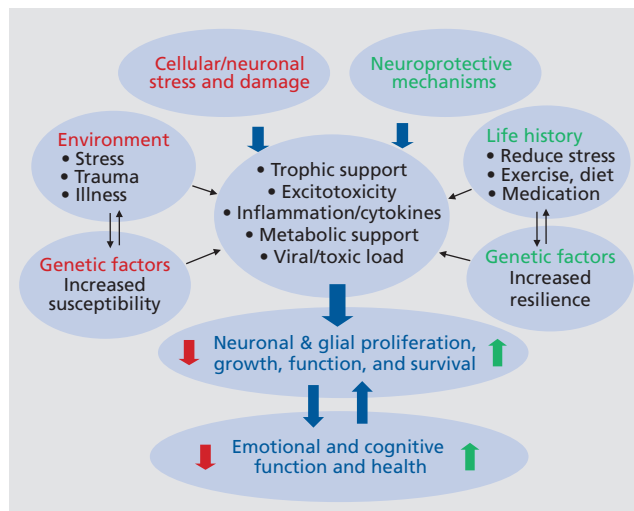


Figure 1. Schematic demonstrating the effects of stress and neuroprotective mechanisms on the proliferation, growth, and survival of neurons and glia. Interactions with environment, genetic factors, and life history also influence these cellular processes, which then regulate emotional and cognitive health or illness. Normal, healthy activity of the brain circuits that underlie emotion and cognition also influence cell survival and function as the expression and function of neurotrophic and neuroprotective mechanisms requires neuronal activity.

including reductions in the number, size, and proliferation of neurons and glia. There is one report that the size of neurons in the major subfields of the hippocampus is reduced,²¹ suggesting a reduction in neuropil that could contribute to decreased hippocampal volume in MDD patients. There were no changes in the numbers of neurons or glia reported in this study or in other qualitative studies, although more subtle synaptic changes have been reported.²²

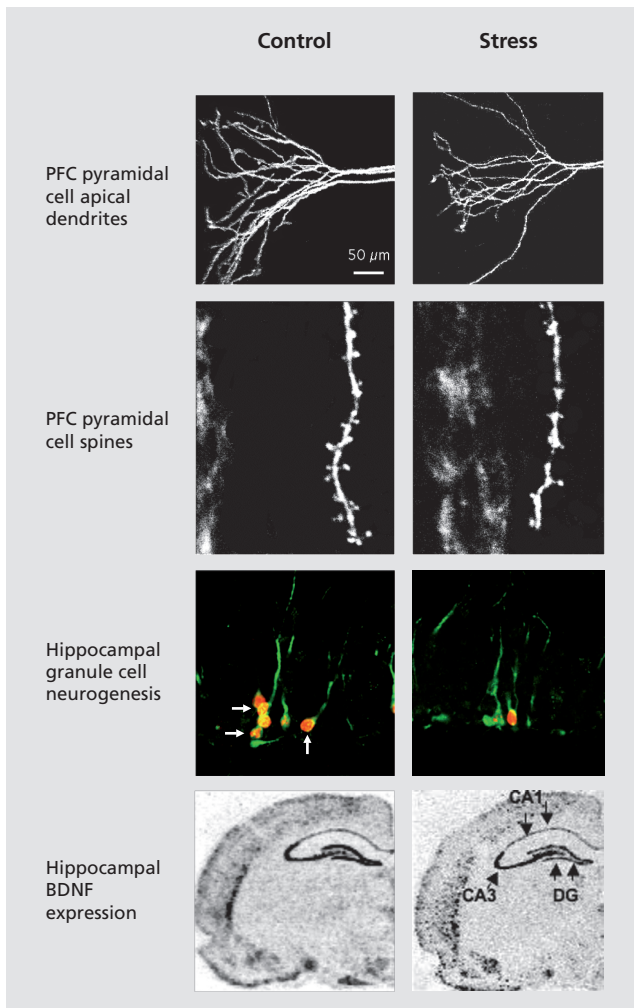


Figure 2. Influence of stress on the morphology and proliferation of neurons and neurotrophic factor expression. Exposure to immobilization stress decreases the number and length of pyramidal cell apical dendrites, and the number of spines in the prefrontal cortex (PFC). Stress also decreases the birth of new neurons and expression of brain derived neurotrophic factor (BDNF) in the adult hippocampus (HP). Images courtesy of Drs G. Aghajanian and R-J. Li.

Studies of the PFC and cingulate cortex have been more extensive, and have shown a reduction in the size of neuronal cell bodies, suggestive of reduced dendritic arborization and complexity.^{23,24} In addition, the most consistent finding in studies of PFC is a decrease in the number of glia in MDD patients.²³⁻²⁵ Reductions of both astrocytes²⁶ and oligodendrocytes^{27,28} have been reported. Given the significant role of glia in providing metabolic support for neurons as well as control of neurotransmitter activity (eg, synthesis and reuptake), it is reasonable to speculate that neuronal atrophy, damage, and hypofunction of PFC could be related to the loss of glia.

Cellular alterations in animal models of depression

Animal models of depression have been used to further elucidate the ultrastructural and molecular alterations that underlie the morphological changes observed in MDD patients. Most of these models are based on acute or chronic-stress paradigms, as stress is a critical factor in the etiology of depression. In addition, these models have been used to demonstrate that antidepressants can reverse or block the effects of stress on cellular morphology, which might contribute to the therapeutic actions of these agents.

Cell morphology

Early studies of cell morphology found that repeated stress causes atrophy of CA3 pyramidal neurons in the hippocampus, characterized by a decreased number and length of apical dendrites.^{29,30} More recent studies have shown that pyramidal neurons in the PFC undergo a similar retraction/atrophy of apical dendrites, and a reduction in spine number in response to immobilization stress (*Figure 2*).³¹ Chronic exposure to high levels of exogenous corticosterone, the rodent equivalent of cortisol, causes a similar atrophy of hippocampal and PFC neurons.^{32,33}

In contrast to most neurological disorders, in which the structural alterations and loss of neurons is permanent, the stress-induced atrophy of hippocampal and PFC neurons is reversible. Most notably, removing animals from stress normalizes the dendritic arborization of pyramidal neurons over a period of several weeks.^{3,32,34} Moreover, chronic administration of certain antidepressants blocks or reverses hippocampal atrophy, even with continued stress exposure.^{29,30} This reversibility supports

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the notion that dendritic alterations represent a type of structural plasticity that has functional consequences.

Cell proliferation

In addition to dendritic atrophy, chronic stress decreases the proliferation of new cells in the adult hippocampus and PFC. The dentate gyrus of the hippocampus is one of the few regions of the brain that continues to give rise to new neurons in adulthood, in rodents as well as non-human primates and humans.^{35,36} Interestingly, the rate of neurogenesis is influenced by environmental and endocrine factors, and stress is one of the most consistent and robust negative regulators (*Figure 2*). The proliferation of new neurons is decreased by different types of stress, including restraint, footshock, maternal separation, predator odor, psychosocial stress, and sleep deprivation, and by administration of exogenous corticosterone.³⁷ In the PFC the proliferation of glia is decreased by exposure to repeated stress³⁸ or corticosterone treatment.³⁹ Chronic stress also decreases the number of glial fibrillary acidic protein (GFAP)-positive astrocytes in the hippocampus.⁴⁰

In contrast, antidepressants increase the proliferation of neurons and glia in the hippocampus and/or PFC, and block or reverse the effects of stress.^{37,38,41,42} These effects require chronic administration (weeks), consistent with the time course for the therapeutic response to antidepressants. Different classes of antidepressants increase cell proliferation in rats, including serotonin selective transporter inhibitors, norepinephrine selective reuptake inhibitors (NSRIs), and electroconvulsive seizures (ECS),^{41,43,44} indicating that this is a common target of ADT.

Behavioral consequences of altered cell morphology

A major question is whether the cellular alterations lead to changes in behavior. This has been addressed by blockade studies (ie, focused irradiation or genetic manipulation), which demonstrate that neurogenesis is required for the actions of antidepressants in certain behavioral models,^{42,45,46} although there are exceptions.^{47,48} Ablation of glia in the PFC decreases sucrose consumption, a measure of anhedonia, indicating a requirement for glial function in this model.⁴⁹ Decreased PFC dendrite arborization in response to stress is also correlated with a reduction in attention set shifting, a PFC-depen-

dent behavior.⁵⁰ These studies demonstrate a causal and/or correlative relationship between cell number and complexity with behavior.

Importance of life stress/trauma: gene-environment interactions

There is also evidence that exposure to traumatic or stressful life events can have a cumulative effect that increases susceptibility or vulnerability to mood disorders⁵¹ (see *Figure 1*). Interactions of stress and genetic factors have also been reported, most notably for lifetime stress and the serotonin (5-HT) transporter short allele polymorphism⁵²; however, a recent meta-analysis suggests that additional studies of this polymorphism are required.⁵³ Studies of genes that increase resilience to stress and mood disorders have also been conducted.⁵⁴ Recent studies have also reported an interaction between early life stress or trauma and neurotrophic factors (see below).

Mechanisms underlying structural alterations and neuroprotection: gene-environment interactions

Cellular and structural alterations in response to stress, depression, and antidepressant medications could result from a number of different mechanisms that alter the proliferation, growth, survival, and function of neurons and glia. These include altered neurotrophic/growth factor support, excitotoxicity, inflammation/cytokines, metabolic/vascular support, viral, and toxic insults. The influence of these factors and insults on cell function and survival could occur rapidly after a single major event or could occur gradually over time with the accumulation of one or more insults, also referred to as allostatic load (*Figure 1*).⁵⁵

The effects of these cellular stressors and insults are also influenced by genetic factors that can either increase susceptibility to cellular damage, or conversely decrease susceptibility and increase resilience and neuroprotection. This complex interaction of gene-environment interactions over the lifespan is thought to contribute to the heterogeneity of depression, other psychiatric illnesses, as well as treatment of these disorders. Characterization of the molecular mechanisms and genetic factors that underlie the structural alterations and that play a key role in neuroprotection will provide

important information for the diagnosis and treatment of depression.

The following sections will discuss the major molecular and cellular mechanisms underlying the actions of stress, depression, and ADT. The latter will include not only chemical antidepressants, but also other strategies that have neuroprotective actions, including exercise. As discussed above, postmortem studies demonstrate a decrease in the size, but not the number, of neurons, indicating that cell death probably does not play a major role in depression. These findings suggest that mechanisms that control maintenance of neuronal size and function, and counteract stress-induced atrophy, such as neurotrophic factors, could be critical mediators. Other important mechanisms to be discussed are glutamate excitotoxicity, apoptosis, and inflammation/immune responses.

Neurotrophic/growth factors

The nerve growth factor (NGF) family has been the focus of much of the work on stress and depression, and the most widely studied member of this family is brain derived neurotrophic factor (BDNF). In addition, several other growth factors, including VEGF, IGF-1, and FGF2 have also been implicated in the effects of stress, depression, and ADT. Because these factors play a critical role in the proliferation, growth, and survival of neurons and glia in the adult brain, their altered expression or function could contribute to the cellular and morphological changes in animal models of depression and in MDD patients. This section will review key evidence demonstrating dysregulation of neurotrophic/growth factors in stress and depression.

Role of BDNF in stress, depression, and ADT

BDNF and related family members, including NGF and neurotrophin-3 (NT-3), influence the proliferation, differentiation, and growth of neurons during development, but are also expressed in the adult brain and play a critical role in the survival and function of mature neurons.⁵⁶ BDNF is expressed at relatively high levels in limbic brain structures implicated in mood disorders, including the hippocampus, PFC, and amygdala, and acts through a transmembrane tyrosine kinase receptor referred to as TrkB. Functional BDNF acts as a dimer to stimulate the intracellular tyrosine kinase domain of TrkB, resulting in autophosphorylation of the receptor and interactions with docking proteins

that lead to activation of one of three major intracellular signaling cascades: the microtubule associated protein kinase (MAPK), the phosphatidylinositol-3 kinase (PI-3K), and the phospholipase-C- γ (PLC γ) pathways (Figure 3).⁸ These cascades have been linked to the neuroprotective effects of BDNF, as well as regulation of cell proliferation, differentiation, and survival.⁵⁶

Stress, depression, and regulation of BDNF

Smith and colleagues were the first to report that exposure to immobilization stress results in a dramatic reduction in levels of BDNF in the rodent hippocampus,⁵⁷ and this effect has been reported with many other types of stress.¹ Decreased expression of BDNF is observed in the major subfields of the hippocampus, including those layers where dendritic atrophy (CA3 pyramidal cell layer) and decreased neurogenesis (dentate gyrus granule cell layer) are observed in response to stress.⁵⁷ Expression of BDNF in the PFC is also decreased by chronic, but not acute stress.⁵⁸ Postmortem studies are consistent with the rodent work, reporting decreased levels of BDNF in the hippocampus of suicide-MDD subjects.⁵⁹⁻⁶¹ These findings provide further support for the hypothesis that the morphological and behavioral abnormalities associated with MDD could result, in part, from decreased BDNF expression.

There are several possible mechanisms that could underlie the regulation of BDNF by stress. This includes a reduction of neuronal firing, as BDNF expression is dependent on activity and Ca²⁺-stimulated gene transcription.⁶² BDNF expression is also decreased by adrenal-glucocorticoids, which are induced by stress and activation of the hypothalamo-pituitary-adrenal (HPA) axis.⁵⁷ There is also evidence that downregulation of BDNF by acute stress is mediated by interleukin-1 β (IL-1 β),⁶³ and epigenetic regulation of BDNF expression in response to chronic social defeat stress.⁶⁴

Genetic studies of BDNF and interactions with stress

A relationship between BDNF, morphology, and behavior is supported by genetic studies of BDNF. Most of this work has focused on a functional polymorphism, Val66Met, that decreases the processing and release of BDNF.⁶⁵ The Met allele has been associated with reduced hippocampal size and decreased memory and executive function in humans.⁶⁵⁻⁶⁷ The met allele has also been asso-

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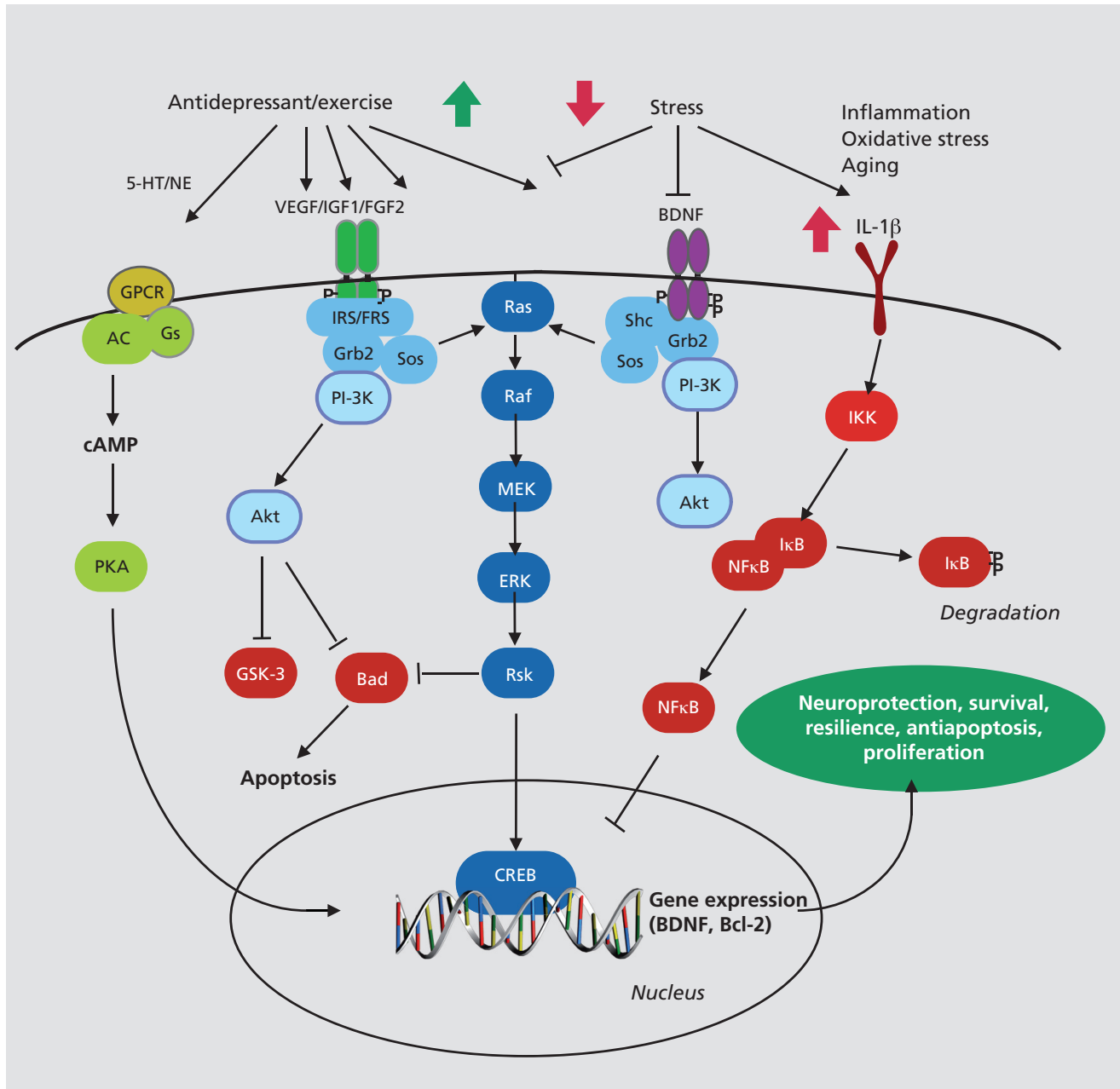


Figure 3. Regulation of neurotrophic/growth factors signaling is decreased by stress and increased by antidepressant treatment. Activation of these pathways leads to neuroprotection, survival, resilience, Antiapoptosis, and proliferation of neurons and glia in limbic brain regions. 5-HT, 5-hydroxytryptamine; NE, norepinephrine; GPCR, G protein coupled receptor; AC, adenylyl cyclase; Gs, stimulatory G protein; cAMP, cyclic adenosine 3',5'-monophosphate; PKA, cAMP-dependent protein kinase; CREB, cAMP response element binding protein; VEGF, vascular endothelial growth factor; IGF-1, insulin-like growth factor-1; FGF2, fibroblast growth factor-2; BDNF, brain derived neurotrophic factor; IRS, insulin receptor substrate; FRS, fibroblast growth factor receptor substrate; Grb2, adaptor protein; Sos, guanine nucleotide exchange factor; PI-3K, phosphatidylinositol 3'-kinase; Akt, protein kinase B, serine/threonine kinase; GSK-3, glycogen synthase kinase-3; Bad, proapoptotic factor; Ras, small guanosine triphosphatase; Raf, serine/threonine kinase; MEK, ERK kinase; ERK, extracellular signal regulated kinase; Rsk, ribosomal S6 kinase; Shc, Src homology domain adaptor protein; IL-1 β , interleukin-1 β ; IKK, kappaB inhibitory protein kinase; I κ B, kappaB inhibitory protein; NF κ B, nuclear factor kappaB; Bcl2, antiapoptotic factor

ciated with smaller volume of cingulate cortex, and this effect is greater in patients with bipolar disorder.⁶⁸ There are also reports that patients carrying the Met allele, either young or aged, have an increased incidence of depression when exposed to stress or trauma.⁶⁹⁻⁷¹ These latter studies highlight the importance of gene x environment interactions in complex, multifactorial illnesses such as depression.

Evidence for a direct relationship between the Met allele and neuronal structure has also been reported in rodent models. In mice expressing the Met allele there is a decrease in the number and length of apical dendrites in both the hippocampus⁷² and PFC,⁷³ similar to the actions of stress.^{73,74}

Although deletion of BDNF is not sufficient to produce depressive-like behaviors, except in female mice,⁷⁵⁻⁷⁷ blockade or reduction of BDNF expression increases the susceptibility to the effects of stress. Exposure of BDNF heterozygous deletion mutant mice to stress or blockade of BDNF-TrkB signaling produces a depressive-like phenotype in the forced swim test.⁷⁸ A gene-environment interaction is also supported by the genetic association studies of the BDNF Met allele discussed above.^{70,71}

A complicating factor in understanding the functions of trophic factors is the possibility that there are opposing, region-specific effects of BDNF. This is based on studies demonstrating that BDNF is increased by stress in the mesolimbic dopamine system and has a depressive effect in the social defeat model, and conversely, that ADT decreases BDNF in this reward pathway.⁷⁹ These findings demonstrate that the expression and function of BDNF, and possibly other trophic factors, is circuit-dependent and that findings in one region cannot be extrapolated to others.

Antidepressants increase BDNF

In contrast to the effects of stress, chronic, but not acute ADT increases the expression of BDNF in the hippocampus and frontal cortex.^{1,80-82} Induction of BDNF is observed with different classes of chemical antidepressants as well as electroconvulsive seizures.^{1,80,82,83} Other agents known to have antidepressant efficacy also increase BDNF expression in the hippocampus, including α -amino-3-hydroxyl-5-methyl-4-isoxazole-propionic acid (AMPA) receptor potentiators, NMDA receptor antagonists, transcranial magnetic stimulation, and exercise.¹ These findings indicate that increased expression of

BDNF is a common target for different therapeutic strategies. Postmortem studies also demonstrate that BDNF levels are increased in the hippocampus of patients receiving antidepressant medication at the time of death, demonstrating the clinical relevance of ADT induction of BDNF.⁵⁹ These effects are thought to occur via activation of cAMP and/or Ca²⁺-dependent BDNF gene transcription that are activated by ADT.⁸⁴⁻⁸⁶

Neuroprotective, neurogenic, and behavioral actions of BDNF

The neuroprotective effects of BDNF have been well documented, primarily in cultured cell systems, but also in vivo. This includes studies demonstrating that BDNF increases survival and has neuroprotective actions in models of hypoxia, ischemia, excitotoxicity, hypoglycemia, and inflammation⁸⁷⁻⁹¹; for reviews see refs 92,93. As discussed above, hippocampal pyramidal cell dendrite complexity is decreased in BDNF Met allele or heterozygous deletion mutants.⁷⁴ Similar effects have been observed in PFC pyramidal cells, and stress does not produce further atrophy of apical dendrites in BDNF heterozygous deletion mutants, indicating that decreased BDNF underlies the effects of stress.⁷³ These findings indicate that a full complement of functional BDNF is required for maintenance of normal dendritic arbor in both the hippocampus and PFC.

BDNF has also been shown to influence hippocampal neurogenesis. Infusions of BDNF increase hippocampal neurogenesis,^{94,95} and BDNF is necessary for the survival of new neurons in response to ADT.⁹⁶ The BDNF receptor, TrkB is also required for antidepressant induction of hippocampal neurogenesis, as well as the behavioral actions of antidepressants.⁹⁷ BDNF has also been implicated in the behavioral actions of ADT. BDNF infusions are sufficient to produce an antidepressant response in rodent behavioral models of depression,⁹⁸⁻¹⁰⁰ and mutant mouse studies demonstrate that BDNF is required for the behavioral actions of antidepressants.⁷⁵⁻⁷⁷ These findings are consistent with the hypothesis that induction of BDNF contributes to the neurogenic and behavioral actions of antidepressants.

Other neurotrophic/growth factors

There is now strong evidence demonstrating a role for several other growth factors in the actions of stress,

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depression, and ADT, including vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF2), and insulin-like growth factor 1 (IGF-1).

VEGF was originally characterized as a vascular permeability factor and an endothelial cell mitogen,¹⁰¹ but is also expressed in the brain in both neurons and glia, and has been shown to play a role in hippocampal neuroplasticity, memory, and neurogenesis.^{102,103} Chronic unpredictable stress decreases the expression of VEGF, as well as its receptor, Flk-1,¹⁰² while ADT increases VEGF expression in the granule cell layer of the hippocampus.¹⁰⁴ Different classes of chemical antidepressants, including SSRI, NSRI, and ECS, increase VEGF expression in the hippocampus, indicating that VEGF is a common downstream target of these treatments.

The opposing actions of stress and ADT on VEGF suggest a possible relationship between neurogenesis and behavior. Stress has a greater effect on newborn cells associated with endothelial cells than nonvascular associated cells.¹⁰² In addition, VEGF is sufficient to induce neurogenesis and produce antidepressant effects in behavioral models of depression, whereas inhibition of Flk-1 blocks the induction of adult neurogenesis and the behavioral effects of ADT.¹⁰⁴

A recent postmortem study found that the expression of FGF2 and its receptors (FGFR2 and FGFR3) are reduced in the PFC and cingulate cortex of MDD patients,¹⁰⁵ and social defeat stress decreases FGF2 in the hippocampus.¹⁰⁶ Conversely, chronic ADT increases the expression of FGF2 in cerebral cortex and hippocampus of rodents^{107,108} and FGF2 infusions are sufficient to produce an antidepressant response in behavioral models.¹⁰⁹ The role of FGF2 in the proliferative actions of ADT, on both neurons and glia, is currently being investigated.

The expression of IGF-1 in the hippocampus is increased by chronic administration of two different monoamine oxidase inhibitor antidepressants.¹¹⁰ In addition to expression in brain, circulating IGF-1, derived primarily from the liver, is actively transported into the brain and is required for the induction of neurogenesis in response to exercise.¹¹¹ Recent studies have also demonstrated that IGF-1 administration, or agents that increase IGF-1 levels, produce antidepressant-like actions in behavioral models of depression.^{98,112,113} Together, these findings suggest that peripheral production and/or the central actions of IGF-1 could be novel targets for the treatment of depression.

Neuroprotective and neurotrophic effects of exercise

Exercise is reported to increase the expression of neurotrophic/growth factors, including BDNF, VEGF, FGF2, and IGF-1.^{111,114-117} In addition, exercise increases neurogenesis in the adult hippocampus, an effect that is dependent on increased expression of IGF-1 and VEGF.^{111,114} IGF-1 has also been shown to underlie the neuroprotective effects of exercise against different types of brain insults.¹¹⁸ In addition to the regulation of these growth factors, exercise has also been shown to influence other neuroprotective mechanisms.¹¹⁹ These positive, neuroprotective actions make exercise one of the key behavioral factors for protecting, or even reversing the damage that can be caused by environmental, physical, and psychological stressors, and even the susceptibility resulting from genetic vulnerabilities (see *Figure 1*).

Glutamatergic excitotoxicity: stress, depression, and ADT

Excess glutamatergic excitotoxicity is one of the major mechanisms underlying neuronal damage and loss in the brain, and has been implicated in the pathophysiology of a variety of disorders, including those resulting from acute insult (eg, stroke induced ischemia or trauma) and neurodegenerative disorders (eg, amyotrophic lateral sclerosis, Huntington's chorea, epilepsy, and Alzheimer's disease).^{120,121} This section discusses evidence for excess glutamate in stress related mood disorders, the cellular mechanisms that contribute to glutamate excitotoxicity, and pharmacological strategies for intervention and treatment.

Excess glutamate in depression and stress

Abnormal glutamate levels and function have been implicated in psychiatric illnesses, including schizophrenia, anxiety, and mood disorders.¹²²⁻¹²⁴ Glutamatergic abnormalities have been reported in the plasma, serum, cerebrospinal fluid (CSF), and brain tissue of individuals suffering from mood disorders.¹²³ Functional in vivo measures of glutamate content in the brain using proton magnetic resonance spectroscopy (H-MRS) show elevated glutamate levels in the occipital cortex of depressed patients, although decreases have been reported in other regions.^{123,125}

Preclinical studies also demonstrate a role for glutamate in the actions of stress. Microdialysis studies have shown that stress increases extracellular levels of glutamate in the PFC and hippocampus,^{126,127} consistent with the possibility that atrophy of CA3 neurons arises in part through increased glutamate neurotransmission.^{128,129} This hypothesis is supported by studies demonstrating that N-methyl-D-aspartic acid (NMDA) receptor antagonists attenuate stress-induced atrophy of CA3-pyramidal neurons.^{29,32,130} Stress or glucocorticoid treatment also increases the susceptibility to other types of neuronal insults, including excitotoxins and ischemia.^{129,131} There are several possible mechanisms that could contribute to the overactivation of glutamate in response to stress and in depression, including a decrease or loss of mechanisms for inactivation of glutamate. Glial cells are responsible for the reuptake and inactivation of glutamate from synaptic and extrasynaptic sites.¹²³ Reductions in the number or function of glia are thought to play a role in the atrophy of limbic brain regions observed in brain imaging studies, as well as decreased neuronal cell body size in postmortem brains of depressed patients.^{123,132,133} Recent studies demonstrate that agents that increase glial reuptake of glutamate, such as riluzole and ceftriaxone, have antidepressant effects in rodent behavioral models and in depressed patients.¹³²⁻¹³⁴

Mechanisms of glutamate excitotoxicity

Glutamate neurotoxicity results from excessive flux of Ca^{2+} via ionotropic receptors, including AMPA, kainate, and NMDA type receptors.^{120,121,123} Uncontrolled elevation of intracellular Ca^{2+} leads to further loss of Ca^{2+} buffering and homeostasis, and then to a cascade of events that contribute to cell damage and death. These include oxidative stress resulting in generation of reactive oxygen species (ROS) and nitric oxide, which results in necrotic cell death characterized by swelling, membrane damage, DNA degradation, and eventually inflammation and cell lysis.^{120,121,135} There are multiple sites for controlling glutamate release and activity at pre- and postsynaptic sites, as well as for buffering intracellular Ca^{2+} that protects against cell damage. These mechanisms are typically overcome only by severe conditions, such as those that would occur during stroke-induced ischemia, prolonged hypoxia, uncontrolled seizures or head trauma. As discussed above, most studies do not report a loss of neurons in post-

mortem tissue from depressed patients, or in animal models. However, excess glutamate is still thought to play a role in psychiatric illnesses, and this has resulted in targeting glutamatergic sites for development of therapeutic agents for mood disorders, as well as for other psychiatric, neurological, and neurodegenerative illnesses.

Glutamate and neuroprotection: therapeutic targets

Glutamate neurotransmission is controlled by a complex system of pre- and postsynaptic receptors, including ionotropic and metabotropic subtypes. In addition, regulation of tropic factor signaling cascades, including extracellular signal-related kinase (ERK), Akt, and cAMP response element binding (CREB) can serve as neuroprotective targets for excitotoxicity. There is also evidence that chronic ADT regulates the phosphorylation, trafficking, and expression of glutamate receptors, providing further evidence that the actions of ADT involves this neurotransmitter system. These topics have been extensively covered by a number of recent reviews.^{121,123,136,137} A brief discussion of the major glutamatergic targets will be discussed here.

One of the key targets for regulation of glutamate is glial reuptake, which is the primary mechanism for inactivation of glutamate neurotransmission. Agents that increase this process, notably riluzole and ceftriaxone, are reported to have antidepressant efficacy in rodent models and in clinical trials.^{123,132,138} These effects are mediated in part by increased expression of glial excitatory amino acid transporters. Riluzole also has several other interesting properties, including the ability to decrease glutamate and increase neurotrophic factor expression, making this an interesting, and potentially useful therapeutic compound. Clinical and preclinical studies are currently underway to further test the therapeutic efficacy and mechanisms underlying the actions of riluzole. Lamotrigine is another compound that acts in part by decreasing glutamate release and is used for treating mood disorders, although with limited efficacy.¹²³ Blockade of the NMDA ionotropic receptor represents another primary target for neuroprotection, although this is a complex issue as glutamate is the major excitatory neurotransmitter in the brain. However, agents that block the NMDA channel, most notably memantine and ketamine, are reported to have antidepressant actions in clinical trials and rodents.^{123,137} The actions of memantine

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have been more modest, with greater effects when coadministered with other antidepressants. However, reports on ketamine have been extraordinary, with several studies demonstrating a rapid and sustained antidepressant response in approximately 60% of patients tested, which have all been resistant to other chemical antidepressants.^{139,140} A single intravenous dose of ketamine, which produces transient and mild psychotomimetic effects, results in an antidepressant response within 6 to 12 hours, and this effect is sustained for at least 7 days. These effects are dramatic compared with all other chemical antidepressants, which require weeks or months of treatment before a therapeutic response is observed. Further studies are needed to identify safer drugs that have rapid antidepressant effects similar to ketamine.

The most direct mechanism to explain the antidepressant action of ketamine is its direct inhibitory effect on NMDA receptors. In particular, the hypothesis that blockade of the extrasynaptic NR2B receptor subtype, which is activated by excess glutamate, underlies the therapeutic action of ketamine has received the most attention. This possibility is supported by a recent study demonstrating that a selective NR2B receptor inhibitor, CP-101,606, produces a rapid antidepressant response in treatment resistant MDD patients.¹⁴¹ Another possible mechanism to account for the rapid actions of these agents is via blockade of NMDA receptors on GABAergic inhibitory neurons, which leads to disinhibition or activation of glutamatergic transmission. The latter possibility is supported by studies in rodents demonstrating that NMDA channel blockers increase BDNF expression in limbic structures, indicating stimulation of neuronal activity,^{142,143} and by a recent report that the behavioral actions of ketamine are blocked by inhibition of AMPA receptor activity.¹⁴⁴

The metabotropic glutamate receptors represent another interesting and diverse set of targets for drug development.^{123,136} Group I receptors, particularly mGluR1/R5 subtypes located at postsynaptic sites as well as on glia, influence both the function and release of glutamate. Drugs acting at these receptors are reported to have anxiolytic effects in rodent models. Group II receptors, mGluR2 and R3, located at presynaptic sites and on glia and regulate glutamate release, have also been targets of interest. Both agonists and antagonists of group II receptors have shown promise, with reports that mGluR2/R3 antagonists have antidepressant actions and agonists

showing anxiolytic and antipsychotic effects. Most promising is a clinical report demonstrating antipsychotic efficacy of an mGluR2/3 agonist.¹⁴⁵

Allosteric AMPA receptor potentiator (ARP) agents make up another interesting group of drugs. These agents do not directly stimulate AMPA receptors, but slow the inactivation or desensitization of the receptors. The idea of using drugs that enhance AMPA receptor function would appear to be counterintuitive given the possibility of an overactive glutamate system. However, preclinical studies of these agents, which were first developed for enhancing cognition, demonstrate positive antidepressant-like effects in rodent models of depression.^{123,146}

Programmed cell death (apoptosis) in stress and depression

Programmed cell death is a critical mechanism for regulation of the appropriate complement of neurons during development, but apoptotic signaling pathways are also regulated in the adult brain and influence the number and function of mature cells. Apoptosis is a highly regulated signaling process, which includes the Bcl-2 family of proteins, cytochrome C, a cytosolic adaptor protein, and caspase activation, which results in energy-dependent death.^{135,147} The Bcl-2 family includes antiapoptotic factors (ie, Bcl-2 and Bcl-xl) that antagonize proapoptotic factors (eg, Bax and Bak). Upon activation of apoptotic pathways, Bax and Bak insert into the mitochondrial membrane and promote the release of cytochrome C, which in turn binds to the apoptotic activator factor (Apaf1), leading to activation of caspases 9 and 3.

Regulation of apoptosis by depression, stress, and ADT

Analysis of postmortem tissue and rodent models has provided some evidence for apoptotic cell death and/or signaling in depression and stress.¹³⁵ There is a postmortem report of low levels of apoptosis in the temporal cortex and hippocampus of depressed patients.¹⁴⁸ Rodent studies demonstrate that social stress increases the number of apoptotic cells in the hippocampus and temporal cortex,¹⁴⁹ and chronic unpredictable stress increases the number of caspase 3 positive neurons in the cerebral cortex.¹⁵⁰ Maternal separation of rats is also reported to increase cell death in the dentate gyrus of hippocampus.¹⁵¹

Genetic association studies have also provided evidence for a link between apoptosis signaling and depression. Polymorphisms of the adaptor protein Apaf1 were found to be associated with major depression.¹⁵² These polymorphisms increase the activity of caspase 9 and would thereby increase the vulnerability of neurons to apoptotic cell death.

There are also several studies that have examined levels of apoptotic signaling proteins in models of stress and ADT. Chronic unpredictable stress is reported to decrease levels of the antiapoptotic factors Bcl-2 and Bcl-xl, but does not influence levels of Bax.¹⁵³ Administration of a high dose of adrenal-glucocorticoids reduces Bcl-2 levels, and this effect corresponds with increased sensitivity to excitotoxic damage.¹⁵⁴ Conversely, chronic ADT increases the expression of Bcl-2 and/or Bcl-xl in limbic brain regions.^{153,155,156} Chronic administration of lithium or valproate also increases Bcl-2 in the hippocampus and PFC.¹⁵⁷ The antiapoptotic actions of lithium and valproate have also been demonstrated in studies of cultured cells.¹⁵⁸⁻¹⁶⁰

Antidepressants also influence other signaling cascades that indirectly influence apoptotic processes. Most notable are the effects of stress and ADT on neurotrophic factors and related signaling cascades, including ERK and Akt, which increase cell survival in part via inhibition of apoptotic, and induction of antiapoptotic factors such as Bcl-2.^{135,161} Finally, it is also notable that certain members of the Bcl-2 family have also been implicated in other cellular functions, including neurotransmission, which could be involved in the actions of stress and ADT.¹⁶²

Mitochondria play a primary role in the storage, processing, and release of proteins involved in apoptosis, and recent studies demonstrate a role for other aspects of mitochondria function in the pathophysiology and treatment of mood disorders.^{154,163}

Inflammation/immune responses

Inflammation and immune responses are major factors contributing to the etiology and pathophysiology of many medical illnesses, including depression and other psychiatric disorders. Inflammation can be caused by other medical conditions, including infection, stroke, trauma, and abnormal or autoimmune responses. However, it is also now clear that psychological stress, such as social stress, can activate the innate immune sys-

tem, elevating cytokine production, and thereby stimulate inflammatory processes.¹⁶⁴⁻¹⁶⁷

Inflammatory and immune processes can lead to multiple actions that have acute protective actions, but that also can have damaging effects on cells and tissue. This includes many of the same actions implicated in the responses to stress and depression, including activation of the HPA axis, alterations of neurotransmitter systems, decreased neurotrophic factor expression, and increased oxidative stress.¹⁶⁷ Depending on the severity and length of the inflammatory response, these effects can result in significant actions on neuronal and glial function and cell survival or death.

There are several proinflammatory cytokines of interest, including IL-1, IL-6, and tumor necrosis factor (TNF) α , that have been implicated in the pathophysiology and treatment of depression. Also of interest are studies of interferon- α , used for the treatment of hepatitis or cancer, which results in depressive-like symptoms in a large number of patients. Here we discuss a few of the most interesting targets for treatment of depression; for a more thorough review see ref 167.

TNF α and depression

One of the most consistently altered proinflammatory cytokines in depressed subjects is TNF α . An inverse correlation between levels of TNF α and treatment response has been reported.^{168,169} TNF α immunotherapy also causes depression, indicating that this cytokine may contribute to the etiology of mood disorders and is not simply a marker for depression (for reviews see refs 168,170). Moreover, a recent large clinical trial using an antibody neutralization approach demonstrated significant antidepressant effects of TNF α reduction.¹⁷¹ This finding is supported by preclinical studies demonstrating that TNF α infusions produce a prodepressive effect,¹⁷² and that TNF α receptor null mutant mice have an antidepressant phenotype in the forced swim and sucrose consumption tests.¹⁷³ Taken together, the preclinical and clinical studies provide strong support for TNF α receptors, particularly TNFR2, as targets for the treatment of mood disorders.

IL-1 β , stress, and depression

There is also strong evidence that the proinflammatory cytokine IL-1 β plays a key role in the pathophysiology of

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stress and depression, and that the IL-1 β signaling is a relevant target for drug development.^{174,175} These findings include: i) clinical studies reporting an increase in serum levels IL-1 β in MDD¹⁷⁶⁻¹⁸⁰; ii) reports that IL-1 β produces stress like effects, including activation of the HPA axis, regulation of monoamines, and behavioral responses in rodent models¹⁸¹; iii) evidence that IL-1 β contributes to conditioned fear and depressive like behavior,¹⁸² and produces anhedonia and disrupts incentive motivation in rodent models¹⁸³; iv) preclinical reports that IL-1 β decreases hippocampal neurogenesis and underlies the decrease observed in response to stress¹⁸⁴; v) our report that CUS-induced anhedonia and decreased neurogenesis produced by is blocked by pharmacological inhibition or null mutation of IL-1 β receptors.¹⁸⁴ Studies are currently underway to determine if blockade of peripheral, as well as central IL-1 β signaling is sufficient to block the effects of stress and produce antidepressant actions.

Interferon and IDO

Recent studies demonstrate that one of the key factors contributing to the depressive actions of inflammation and activation of the innate immune system is the induction of a tryptophan degradative enzyme, indoleamine 2,3-dioxygenase (IDO). Chronic inflammation and infection can lead to sustained induction of interferon, which is then responsible for the increased levels of IDO. The induction of IDO then results in diversion of tryptophan from the synthesis of serotonin to kynurenic acid, which can be further converted to toxic metabolites, most notably quinolinic acid. Evidence for IDO in depression is supported by studies demonstrating that decreased levels of tryptophan and increased kynurenic acid is associated with inflammation and depression.¹⁸⁵ Increased IDO has also been positively correlated with depression, although a direct causal relationship has not been demonstrated.

A recent study has now provided direct evidence that induction of IDO underlies the depressive behaviors caused by inflammation/activated immunologic conditions. This work was conducted using a bacterial immune activation model, Bacille Calmette-Guerin (BCM), which induces a long-lasting induction of interferon and results in depressive behaviors in animal models.^{185,186} The results demonstrate that BCM-mediated immobility in the forced

swim test is reversed by an IDO inhibitor, 1-methyltryptophan, and in mice that are deficient in IDO.¹⁸⁵ In addition, BCM also increases the expression of a downstream enzyme, 3-hydroxyanthranilic acid oxygenase (3-HAO) that is involved in the synthesis of quinolinic acid. These studies indicate that an IDO inhibitor, and possibly an inhibitor of 3-HAO, could have efficacy for the treatment of depression and related mood disorders.

Summary and future directions

Significant advances have been made in characterizing the neuronal and glial damage, or structural alterations, at the cellular and anatomical levels in stress-related mood disorders and other psychiatric illnesses, and in elucidating the molecular signaling pathways and mechanisms that underlie these changes. However, this work is still at a relatively early stage, and a more complete characterization of these complex alterations and signaling mechanisms will require extensive resources and time. Moreover, identification of genetic polymorphisms that impact these pathways and systems and that influence susceptibility or resilience to illness is a major area of research that will continue to develop and unfold. When combined with studies of environmental risk factors and lifetime history of stress, this work will define and describe the mechanisms underlying individual variations of illness.

Together, the results of this work can be used to formulate a comprehensive approach for the prevention and treatment of psychiatric illnesses. Changes in lifestyle and behavior can reduce stress and exposure to environmental factors that influence cellular risk and damage and prevent illness. These approaches, as well as behavioral interventions that enhance the activity and function of specific neural circuits, and thereby provide protection, can also be used once a person has become ill. Development of therapeutic agents that target neuroprotective mechanisms, combined with genetic information will ultimately provide tailored approaches for highly specific and efficacious treatments for depression and other illnesses. \square

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Daño y protección neuronal en la fisiopatología y el tratamiento de la enfermedad psiquiátrica: el estrés y la depresión

El haber descubierto que el estrés y la depresión, al igual que otras enfermedades psiquiátricas, se caracterizan por alteraciones estructurales, y que estos cambios se deben a atrofia y pérdida de neuronas y glía en regiones y circuitos límbicos específicos ha contribuido a un cambio fundamental en la comprensión de estas enfermedades. Estos cambios estructurales se acompañan de una falta de regulación de los mecanismos de señales neuroprotectoras y neurotróficas, los cuales son requeridos para la maduración, crecimiento y supervivencia de las neuronas y la glía. A la inversa, las intervenciones conductuales y terapéuticas pueden revertir estas alteraciones estructurales mediante la estimulación de las vías neuroprotectoras y neurotróficas y a través del bloqueo de los efectos dañinos, excitotóxicos e inflamatorios del estrés. La exposición a lo largo de la vida a estresores celulares y ambientales, y las interacciones con factores genéticos contribuyen a la susceptibilidad o a la resiliencia. Esta interesante área de investigación abriga potenciales esperanzas para favorecer la dilucidación de la fisiopatología de las enfermedades psiquiátricas y el desarrollo de nuevas intervenciones terapéuticas.

Lésions et protection neuronales dans la physiopathologie et le traitement des maladies psychiatriques : stress et dépression

Notre compréhension du stress et de la dépression, comme d'autres maladies psychiatriques, a été profondément transformée en découvrant que ces maladies sont caractérisées par des modifications structurales résultant de l'atrophie et de la perte des neurones et de la glie dans des régions et des circuits limbiques spécifiques. Ces modifications structurales s'accompagnent d'une dysrégulation des mécanismes de signalisation neurotrophiques et neuroprotecteurs nécessaires à la maturation, la croissance et la survie des neurones et de la glie. À l'opposé, des interventions comportementales et thérapeutiques peuvent inverser ces modifications structurales en stimulant les voies neuroprotectrices et neurotrophiques et en bloquant les effets lésionnels, excitotoxiques et inflammatoires du stress. L'exposition durant la vie aux agents stressants cellulaires et environnementaux et les interactions avec des facteurs génétiques participent à la susceptibilité individuelle ou à la résilience. Ce domaine de recherche passionnant est prometteur et devrait permettre d'expliquer plus précisément la physiopathologie des maladies psychiatriques et de participer au développement de nouveaux traitements.

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